under typical amide bond forming conditions to give the amide **5.2** as described above, Scheme **1**. Preferably the acid **5.1** is first treated with EDC and n-hydroxybenzotriazole in DMF and then the amine **3.4** is added in DMF followed by N-methyl morpholine to give the amide **5.2**. Reduction of the amide under the same catalytic hydrogenation conditions as

5   described above in Scheme 3 gives the free amine **5.3**. The amine is further treated with chloroacetyl chloride to provide the chloro compound **5.4**. Preferably treatment with the chloroacetyl chloride is performed in ethyl acetate and water mixture in the presence of a base such as potassium hydrogen carbonate. The chloro compound **5.4** is treated with hydrochloric acid in dioxane and ethyl acetate to give the salt of the free amine **5.5** . The salt **5.5** is then

10   treated with a nitro-sulfonyl chloride **1.4** in THF and water in the presence of a base such as potassium carbonate to give the sulfonamide **5.6**. Alternatively the free amine **5.5** is treated with a chloroformate **1.4** in the presence of a base such as triethylamine to afford the carbamate. Methods for the preparation of carbamates are also described below, Scheme **98**. Compound **5.6** is then treated with the amine **5.7** to give the secondary amine **5.8**. Preferably

15   the chloride is refluxed in the presence of the amine **5.7** in THF.

The reactions shown in Scheme **5** illustrate the preparation of the compound **5.8** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **6** depicts the conversion of **5.8** in which A is [OH], [SH], [NH], Br etc, into the

20   phosphonate ester **1** in which X is a direct bond. In this procedure **5.8** is converted, using the procedures described below, Schemes **47-99**, into the compound **1**.

In the preceding and following schemes, the conversion of various substituents into the group link-P(O)(OR^1)$_2$ can be effected at any convenient stage of the synthetic sequence, or in the

25   final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group link-P(O)(OR^1)$_2$.
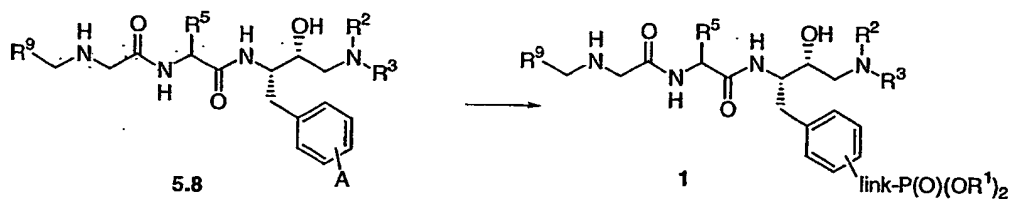
30   In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical

transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 99).

Scheme 5

3.4   5.1   5.2

5.3   5.4   5.5

1.4   5.6   5.7   5.8

Scheme 6

5.8   1

5
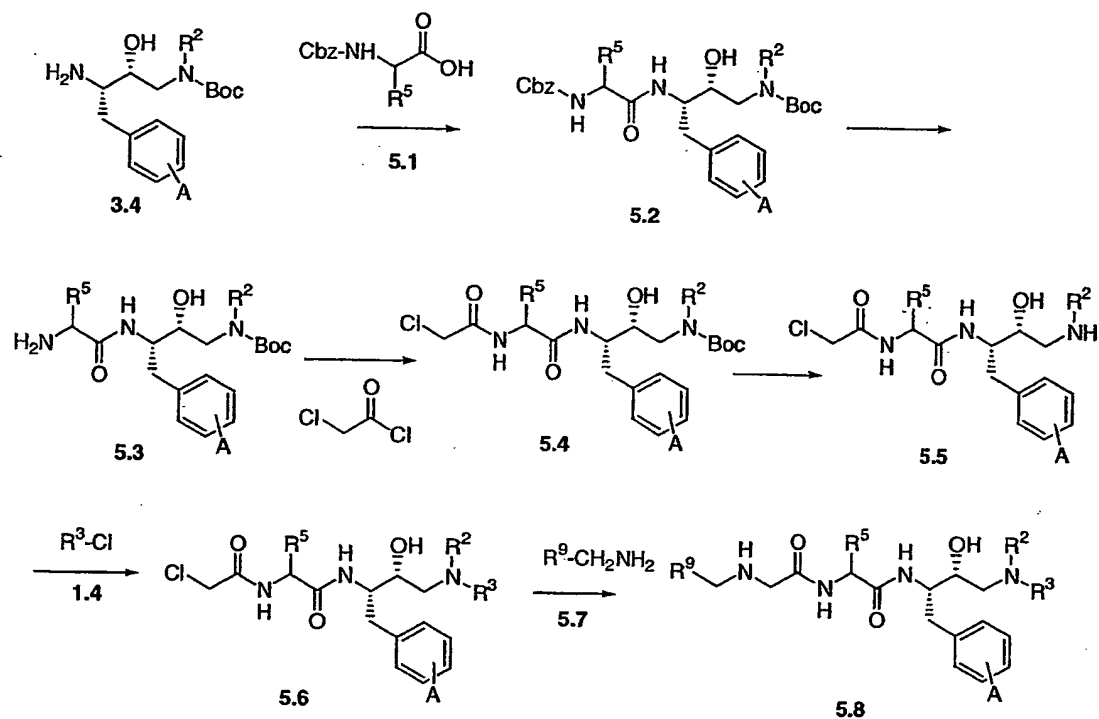
Preparation of the phosphonate ester intermediates 1 in which X is a sulfur.

The intermediate phosphonate esters **1**, in which X is sulfur, the R$_4$COOH group does not contain a amine group, and in which substituent A is either the group link-P(O)(OR^1)$_2$ or a
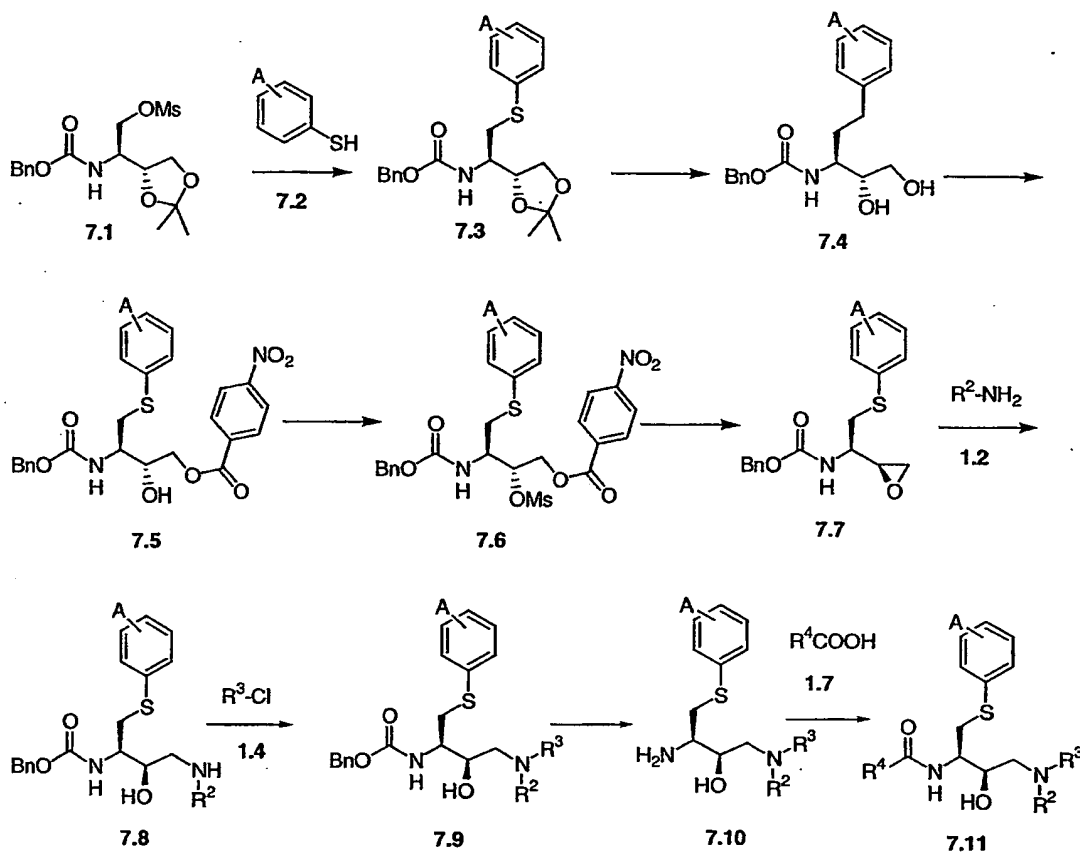10 precursor such as [OH], [SH], [NH], Br etc, are prepared as shown in Schemes 7-9.

Scheme 7 illustrates one method for the preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, methanesulfonic acid 2-

5   benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, 7.1, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol 7.2 to afford the thioether 7.3. The preparation of thiol 7.2 is described in Schemes 63-72. The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether

10   7.3. Preferably the mesylate 7.1 is reacted with an equimolar amount of the thiol, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product 7.3. The 1,3-dioxolane protecting group present in the compound 7.3 is then removed by acid catalyzed hydrolysis or

15   by exchange with a reactive carbonyl compound to afford the diol 7.4. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound 7.3 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane 7.3 is dissolved in aqueous

20   methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product 7.4. The primary hydroxyl group of the diol 7.4 is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base.

25   Preferably, equimolar amounts of the diol 7.4 and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester 7.5. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the

30   corresponding sulfonyl ester 7.6. Preferably, equimolar amounts of the carbinol 7.5 and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate 7.6. The compound 7.6 is then subjected to a hydrolysis-

cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group

present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation,

spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect

this transformation, the sulfonyl ester **7.6** is reacted with an alkali metal hydroxide or

5   tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate **7.6** is

reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour,

to afford the oxirane **7.7**.

The oxirane compound **7.7** is then subjected to regiospecific ring-opening reaction by

treatment with a secondary amine **1.2**, to give the aminoalcohol **7.8**. The amine and the

10   oxirane are reacted in a protic organic solvent, optionally in the additional presence of water,

at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the

product **7.8**. Preferably, equimolar amounts of the reactants **7.7** and **1.2** are reacted in aqueous

methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford

the aminoalcohol **7.8**. The free amine is then substituted by treatment with an acid,

15.   chloroformate or sulfonyl chloride as described above in Scheme **1** to give the amine **7.9**. The

carbobenzyloxy (cbz) protecting group in the product **7.9** is removed to afford the free amine

7.10. Methods for removal of cbz groups are described, for example, in Protective Groups in

Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods

include catalytic hydrogenation and acidic or basic hydrolysis. For example, the cbz-protected

20   amine **7.9** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or

alcoholic solvent, to yield the free amine **7.10**. Preferably, the cbz group is removed by the

reaction of **7.9** with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to

afford the amine **7.10**. The amine **7.10** so obtained is next acylated with a carboxylic acid or

activated derivative **1.7**, using the conditions described above in Scheme **1** to afford the

25   product **7.11**

Scheme 7

Scheme **8** illustrates an alternative preparation of the compounds **1** in which the substituent X is S, and in which the group A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such

5   as [OH], [SH] Br etc. In this sequence, 4-amino-tetrahydro-furan-3-ol, **8.1**, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R^{4}COOH, **1.7**, using the conditions described above for in Scheme **1** for the preparation of amides, to afford the amide **8.2**. The amide product **8.2** is then transformed, using the sequence of reactions shown in Scheme **8**, into the isoxazoline compound **8.5**. The

10   hydroxyl group on the tetrahydrofuran moiety in **8.2** is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane. Preferably, the hydroxy amide **8.2** is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester **8.3**. The product **8.3**, bearing a suitable sulfonyl ester leaving group, is

15   then subjected to acid-catalyzed rearrangement to afford the isoxazoline **8.4**. The

rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic

anhydride, in the presence of a strong acid catalyst. Preferably, the mesylate 8.3 is dissolved in

an acylating agent such as acetic anhydride at about 0°C, in the presence of about 5 mole % of

a strong acid such as sulfuric acid, to afford the isoxazoline mesylate 8.4. The leaving group,

5   for example a mesylate group, is next subjected to a displacement reaction with an amine. The

compound 8.4 is reacted with an amine 1.2, as defined in Chart 3, in a protic solvent such as

an alcohol, in the presence of an organic or inorganic base, to yield the displacement product

8.5. Preferably, the mesylate compound 8.4 is reacted with an equimolar amount of the amine

1.2, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient

10   temperature, to afford the product 8.5. The product 8.5 is then treated with R^3Cl, chart 6 as

described above in Scheme 1 to afford the amine 8.6. The compound 8.6 is then reacted with

a thiol 7.2 to afford the thioether 7.11. The reaction is conducted in a polar solvent such as

DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford

the product 7.11. Preferably, the isoxazoline 8.6 is reacted, in methanol, with an equimolar

15   amount of the thiol 7.2, in the presence of an excess of a base such as potassium bicarbonate,

at ambient temperature, to afford the thioether 7.11.

The procedures illustrated in Scheme 7-8 depict the preparation of the compounds 7.11 in

which X is S, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a

20   precursor thereto, such as [OH], [SH] Br etc, as described below. Scheme 9 illustrates the

conversion of compounds 7.11 in which A is a precursor to the group link-$P(O)(OR^1)_2$ into

the compounds 1 in which X=S. Procedures for the conversion of the substituent A into the

group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes 47 – 99).


25   Scheme 9a-9b depicts the preparation of phosphonate esters 1, in which X is sulfur, the

R_4COOH group does contain a amine group, and in which substituent A is either the group

link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The amine 7.10 prepared in

Scheme 7 is treated with the CBZ protected amine 5.1 using the same conditions described in

Scheme 5 for the preparation of 5.2 to give CBZ amine 9a.1. Removal of the CBZ group as

30   described in Scheme 5 to give 9a.2 followed by treatment with chloroacetyl chloride as

described in Scheme 5 gives chloride 9a.3. The chloride 9a.3 is then treated with the amine

5.7 to give the amine 9a.4 as described in Scheme 5.

The reactions shown in Scheme **9a** illustrate the preparation of the compound **9a.4** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **9b** depicts the conversion of **9a.4** in which A is [OH], [SH], [NH], Br

5   etc, into the phosphonate ester **1** in which X is sulfur. In this procedure **9a.4** is converted, using the procedures described below, Schemes **47-99**, into the compound **1**.
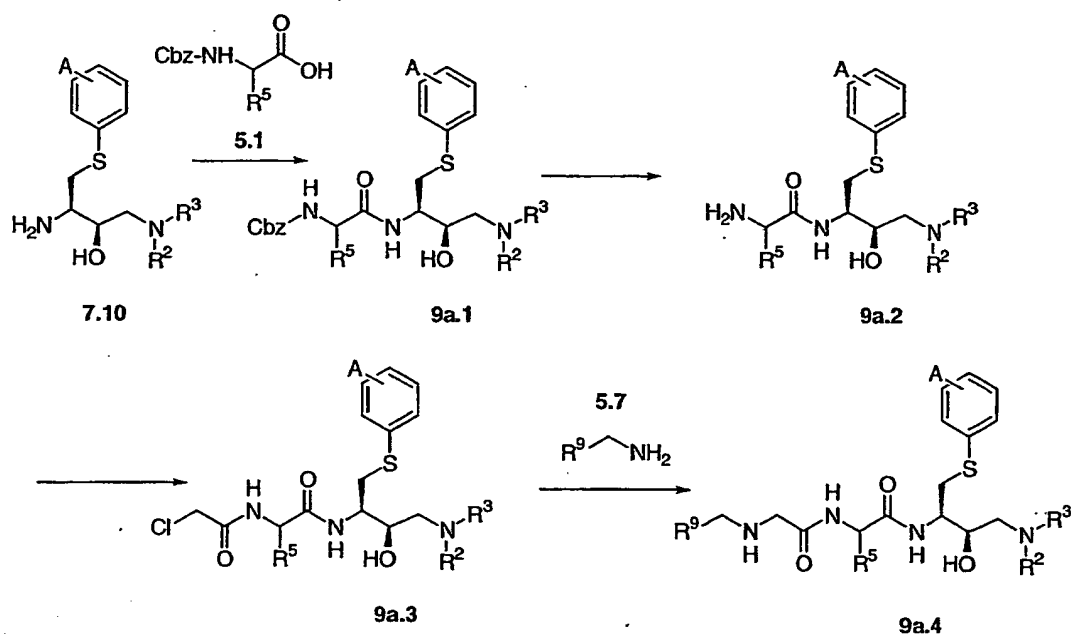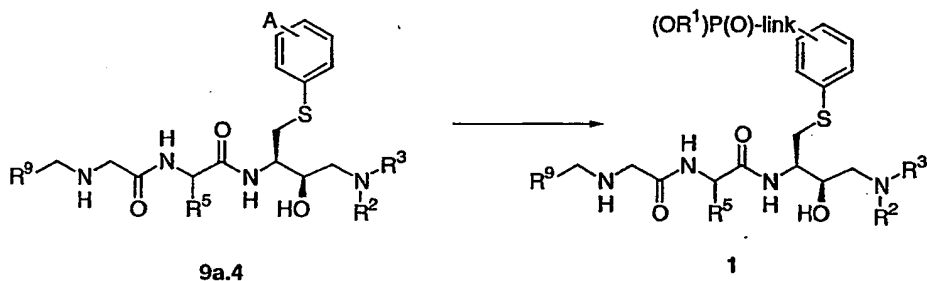
Scheme 8
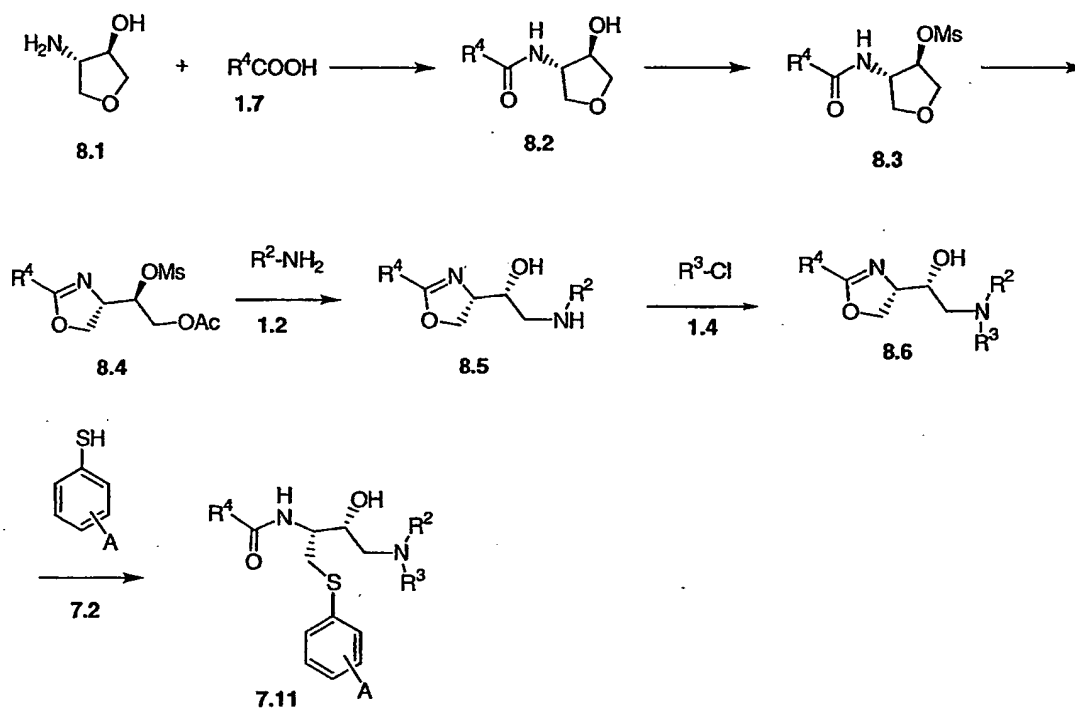
Scheme 9
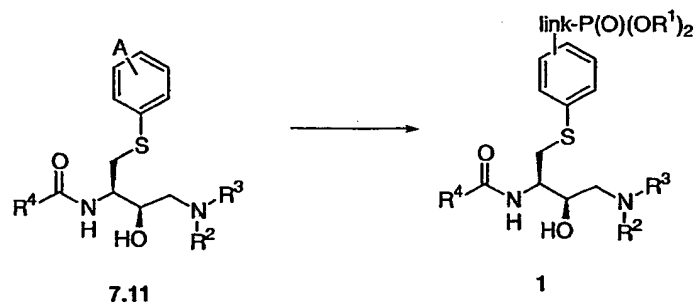
Scheme 9a

7.10   9a.1   9a.2

9a.3   9a.4

Scheme 9b

9a.4   1

Preparation of the phosphonate ester intermediates 2 and 3 in which X is a direct bond

5

Schemes **10-12** illustrate the preparation of the phosphonate esters **2** and **3** in which X is a direct bond and the R$_4$COOH group does not contain a primary or secondary amine group. As shown in Scheme **10**, the epoxide **10.1**, prepared as described in J. Med. Chem 1994, 37, 1758 is reacted with the amine **10.2** or **10.5**, in which the substituent A is either the group

10   link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amine **10.3** and **10.6** respectively. The reaction is performed under the same conditions as described

above, Scheme **1** for the preparation of the amine **1.3**. The preparation of the amines **10.2** is described in Schemes **73-75** and amines **10.5** in schemes **76-78**. The products **10.3** and **10.6** are then transformed, using the sequence of reactions described above, Scheme **1**, for the conversion of the amine **1.3** into the amide **1.8**, into the aminoamide **10.4** and **10.7**

5   respectively.

An alternative route to the amines **10.4** and **10.7** is shown in Scheme **11** in which sulfonyl ester **11.1** prepared according to Chimia 1996, 50, 532 is treated under conditions described in Scheme **2** with the amines **10.2** or **10.5** to give the amines **11.2** or **11.3** respectively. These

10 amine products are then converted as described above, Scheme **2**, into the amides **10.4** and **10.7** respectively.

The reactions shown in Scheme **10** and **11** illustrate the preparation of the compounds **10.4** and **10.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as

15 [OH], [SH], [NH], Br etc. Scheme **12** depicts the conversion of these compounds **10.4** and **10.7** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **2** and **3** respectively, in which X is a direct bond. In this procedure, the amines **10.4** and **10.7** are converted, using the procedures described below, Schemes **47-99**, into the compounds **2** and **3** respectively.

Scheme 10

Scheme 11

Scheme 12

10.4   2
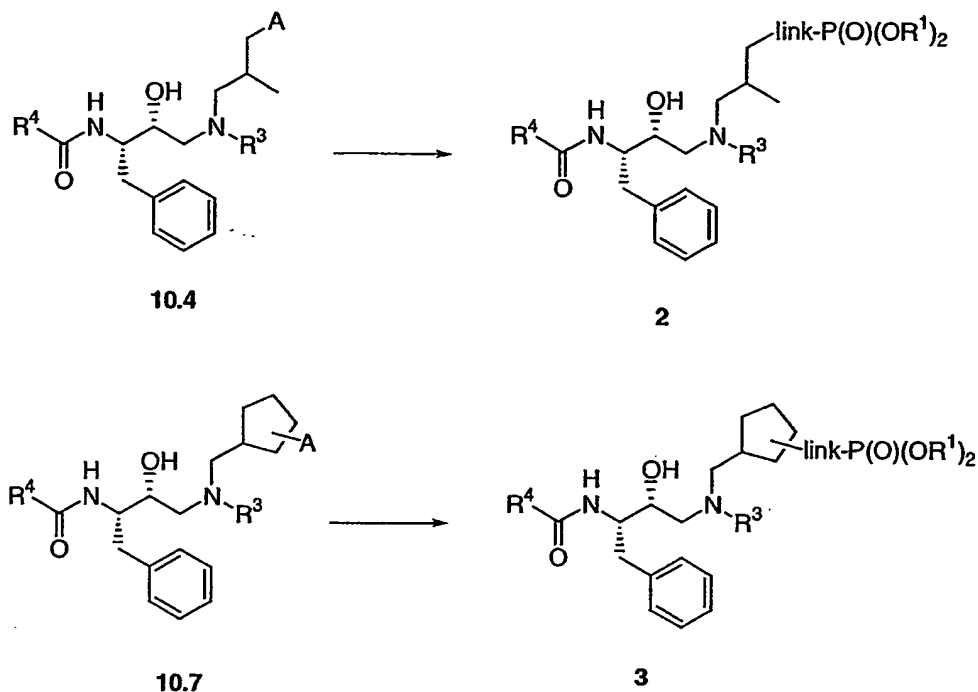

10.7   3
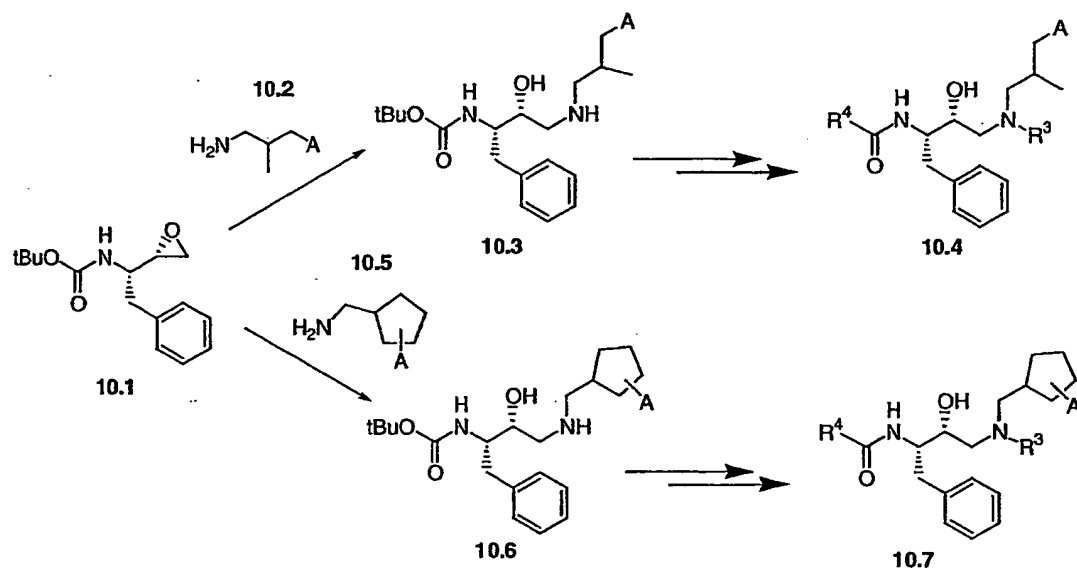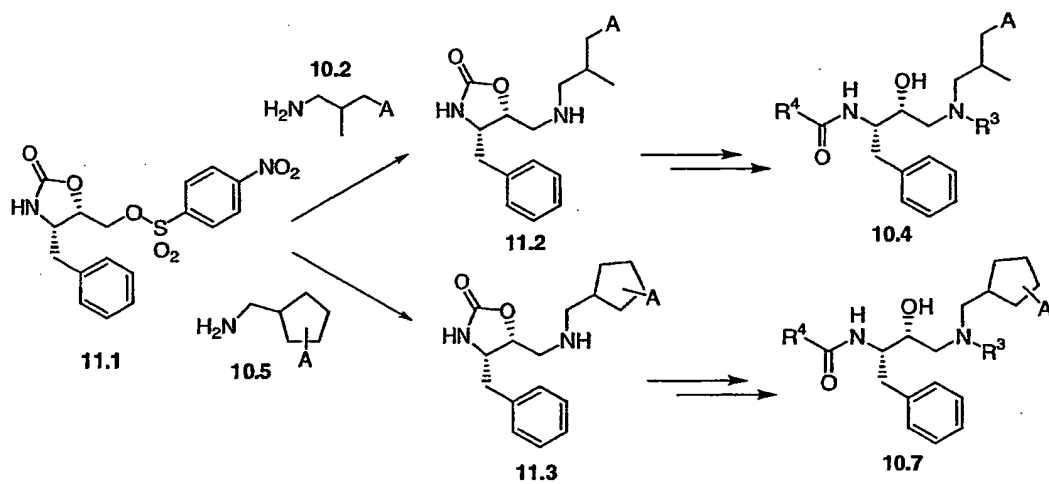
Schemes **13-14** illustrates the preparation of the phosphonate esters **2** and **3** in which X is a direct bond and the R$_4$COOH group contains an amine. The epoxide **13.1**, prepared as described in US 6391919B1, or J. Org. Chem. 1996, 61, 3635 is reacted, as described above, (Scheme **1**) with the amine **10.2** or **10.5**, in which substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, to give the amino alcohols **13.2** and **13.4**, respectively. These amines are then converted as described in Scheme **3** for the conversion of **3.2** into **3.4** and Scheme **5** for the conversion of **3.4** into **5.8**, into the amine products **13.3** and **13.5** respectively.

The reactions shown in Scheme **13** illustrate the preparation of the compounds **13.3** and **13.5** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **14** depicts the conversion of the compounds **13.3** and **13.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **2** and **3** in which X is a direct bond. In this procedure, the compounds **13.3** and **13.5** are converted, using the procedures described below, Schemes **47-99**, into the compounds **2** and **3** respectively.
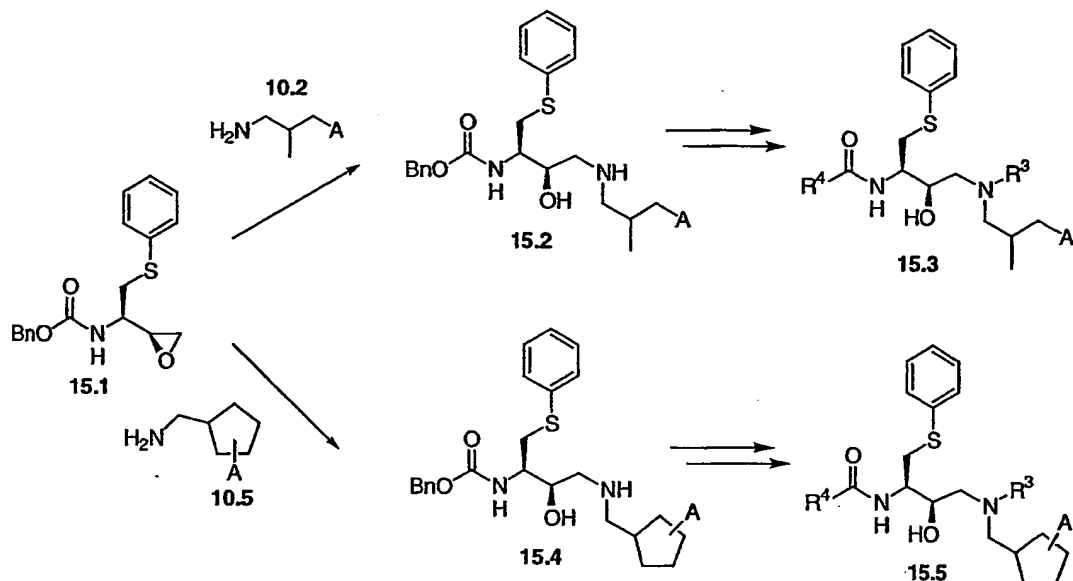
Scheme 13
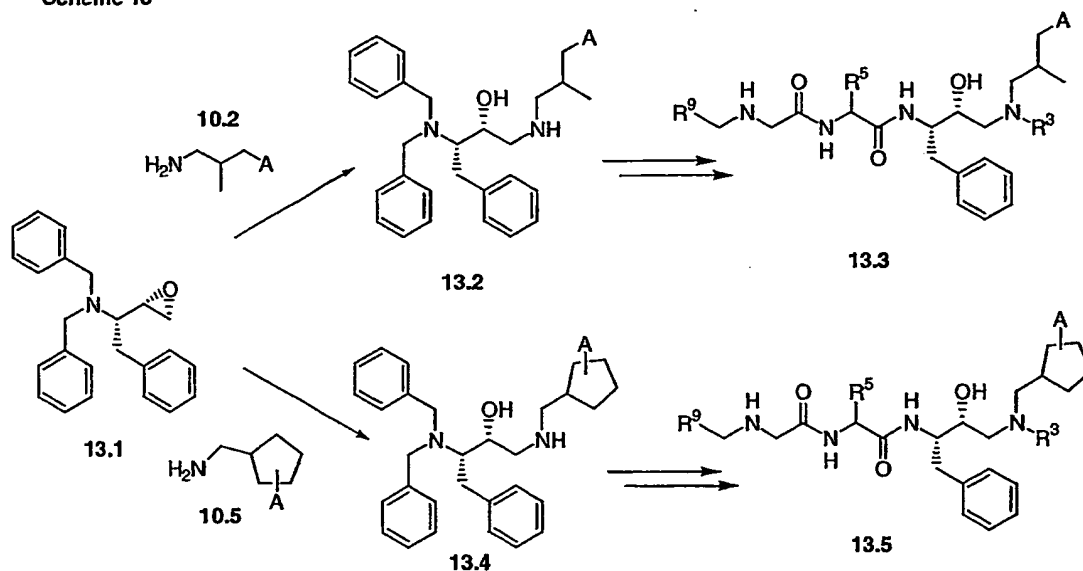
Scheme 14
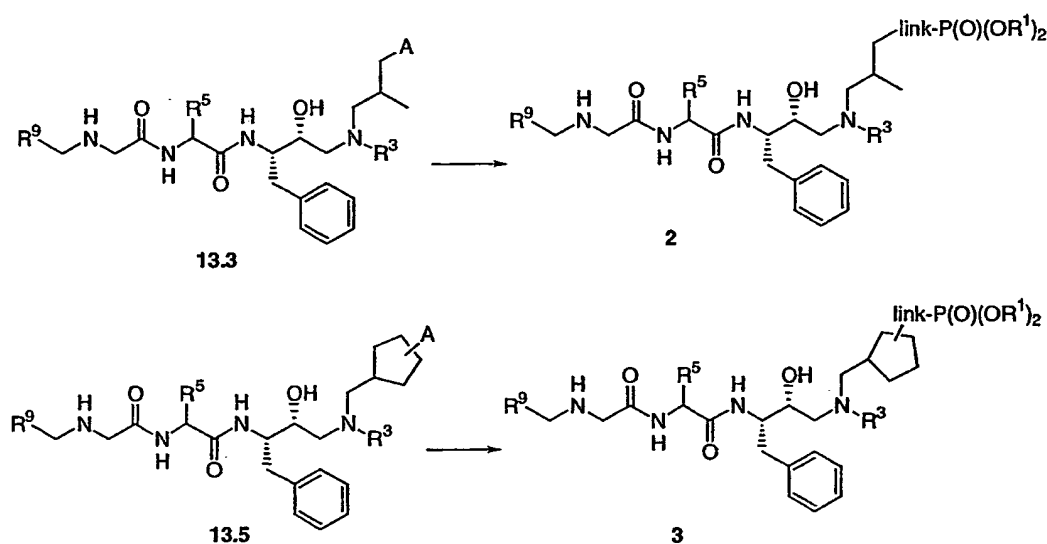
Preparation of the phosphonate ester intermediates 2 and 3 in which X is a sulfur

5   The intermediate phosphonate esters **2** and **3**, in which the group A is attached to a sulfur
linked aryl moiety, and the R$_4$COOH group does not contain an amine group, are prepared as
shown in Schemes **15-17**. In Scheme **15**, epoxide **15.1** is prepared from mesylate **7.1** using
the conditions described in Scheme **7** for the preparation of **7.7** from **7.1**, except incorporating

thiophenol for thiol **7.2.** The epoxide **15.1** is then treated with amine **10.2** or amine **10.5,** in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **7,** to give the amines **15.2** and **15.4.** Further application of Scheme **7** on the amines **15.2** and **15.4** yields the alcohols **15.3** and **15.5** respectively.

5   Alternatively, Scheme **16** depicts the preparation of **15.3** and **15.5** using the mesylate **8.4.** The amines **10.2** and **10.5** are reacted with mesylate **8.4** under conditions described in Scheme **8** to give amines **16.1** and **16.2** respectively. Further modification of **16.1** and **16.2** according to the conditions described in Scheme **8** then affords alcohols **15.3** and **15.5** respectively.

10   The reactions shown in Scheme **15-16** illustrate the preparation of the compounds **15.3** and **15.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **17** depicts the conversion of **15.3** and **15.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **2** and **3** in which X is sulfur. In this procedure **15.3** or **15.5** is converted, using the procedures described below, Schemes **47-99,**
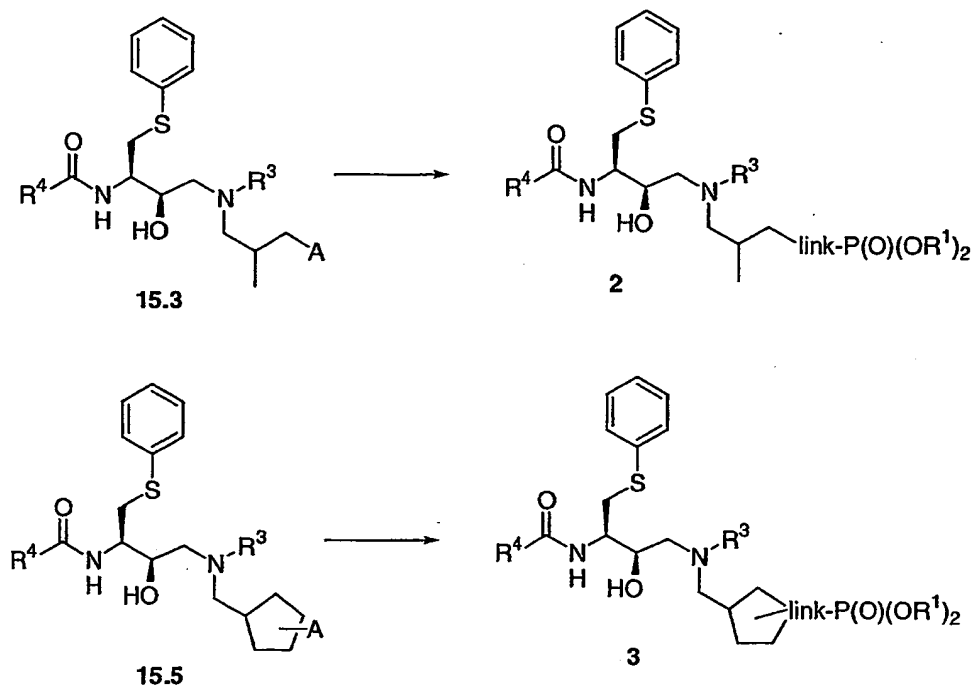
15   into the compound **2** and **3.**

Scheme 15

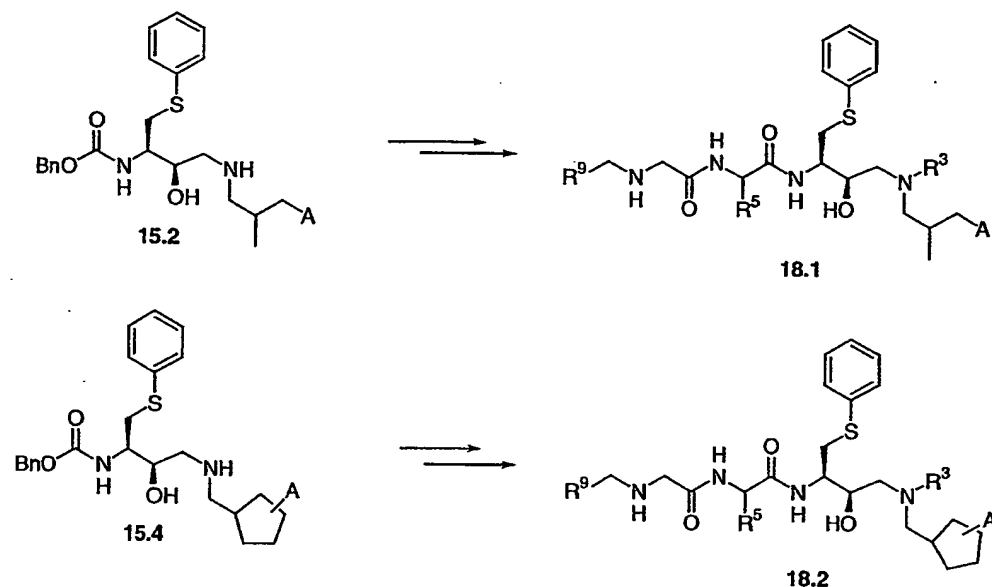**Scheme 16**

Scheme 17

15.3   2

15.5   3
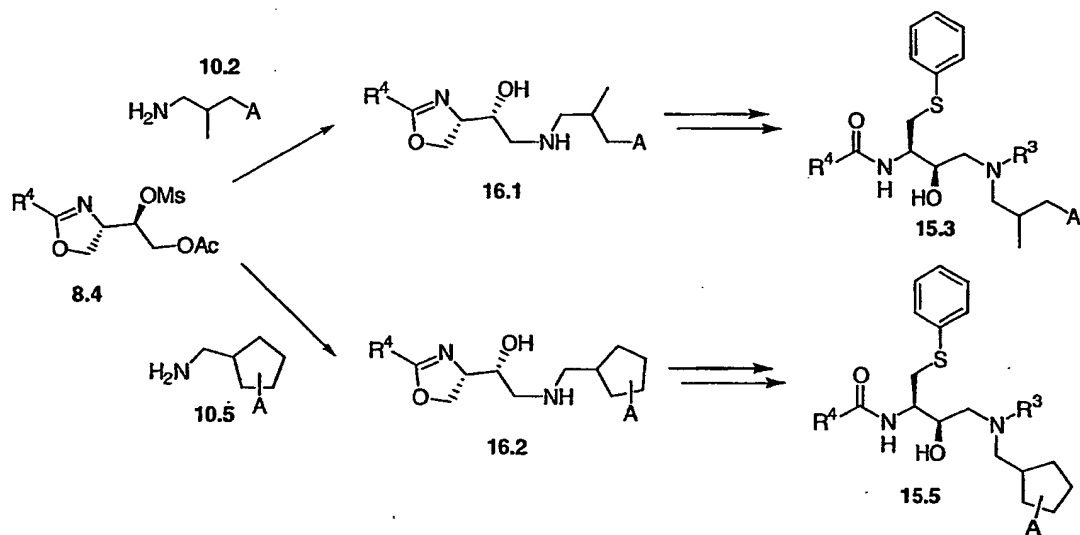
Scheme **18-19** depict the preparation of phosphonate esters **2** and **3**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains a amine group. The

5   amines **15.2** and **15.4,** in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, prepared in Scheme **15**, are converted using the same conditions described in Scheme **7** for the preparation of the amine **7.10** from **7.8** and Scheme **9a** for the preparation of **9a.4** from **7.10** to give **18.1** and **18.2** respectively.

10   The reactions shown in Scheme **18** illustrate the preparation of the compound **18.1** and **18.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **19** depicts the conversion of **18.1** and **18.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **2** and **3** respectively in which X is sulfur. In this procedure **18.1** and **18.2** are converted, using the procedures described below, Schemes

15   **47-99**, into the compounds **2** and **3**

Scheme 18

15.2

18.1

15.4

18.2

Scheme 19

18.1

2

18.2

3
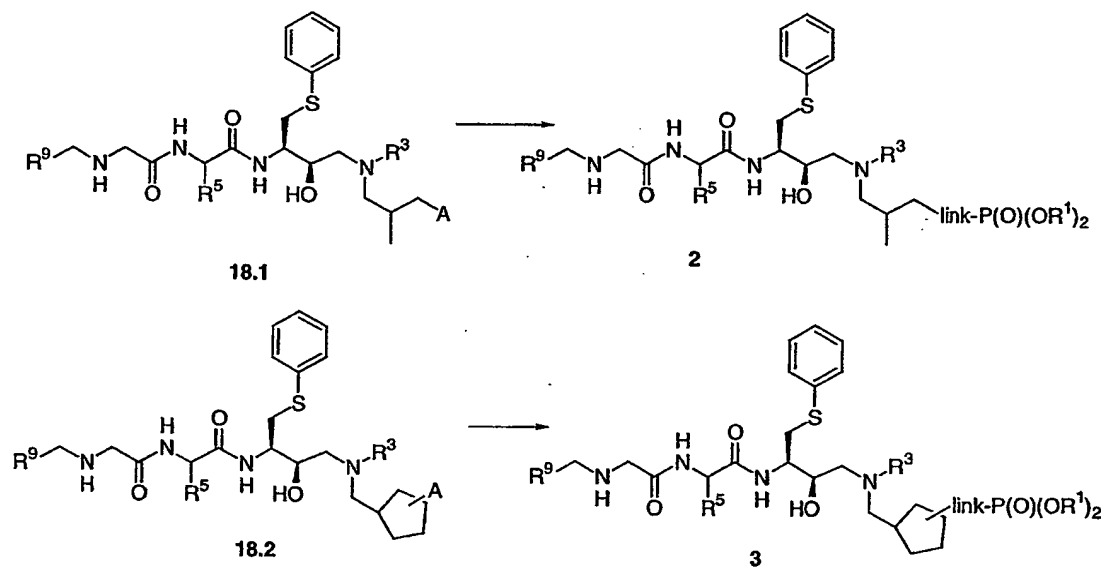
Preparation of the phosphonate ester intermediates 4 in which X is a direct bond
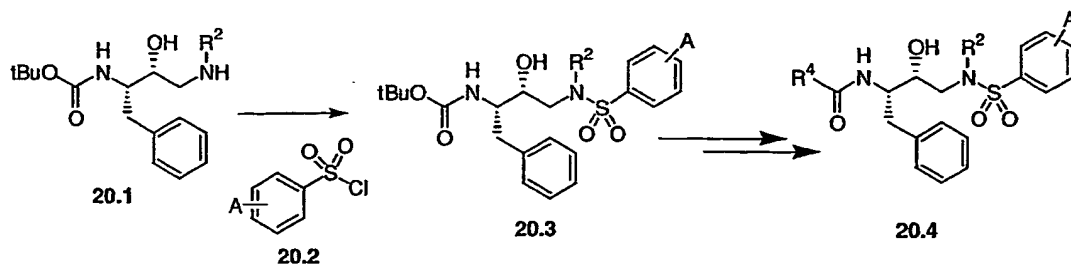
5   Schemes 20-22 illustrate the preparation of the phosphonate esters **4** in which X is a direct
bond and the R group does not contain a primary or secondary amine group. As shown in
Scheme **20**, the amine **20.1** is reacted with the sulfonyl chloride **20.2** in which the substituent
A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, to

afford the product **20.3**. The reaction is performed under the same conditions as described above, Scheme **1** for the preparation of the sulfonamide **1.5**. Amine **20.1** is prepared by treatment of epoxide **10.1** with the amine **1.2** as described in Scheme **1** for the preparation of **1.3**. The preparation of sulfonyl chloride **20.2** is described in Schemes **92-97**. The product

5   **20.3** is then transformed, using the sequence of reactions described above, Scheme **1**, for the conversion of the amide **1.5** into the amide **1.8**, into the product **20.4**.

An alternative route to the product **20.4** is shown in Scheme **21** in which amine **11.1** is treated under conditions described in Scheme **2** with the amine **1.2** to give the amine **21.1**. The amine

10   **21.1** is then sulfonylated with **20.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **2**, to afford the product **21.2**. The product **21.2** is then converted as described above, Scheme **2**, into the sulfonamide **20.4**.

15   The reactions shown in Scheme **20** and **21** illustrate the preparation of the compound **20.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **22** depicts the conversion of this compounds **20.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **4** respectively, in which X is a direct bond. In this procedure, the amines **20.4** is converted, using the procedures described below,
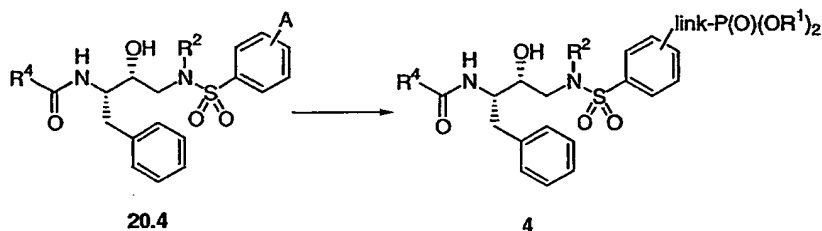
20   Schemes **47-99**, into the compounds **4**.

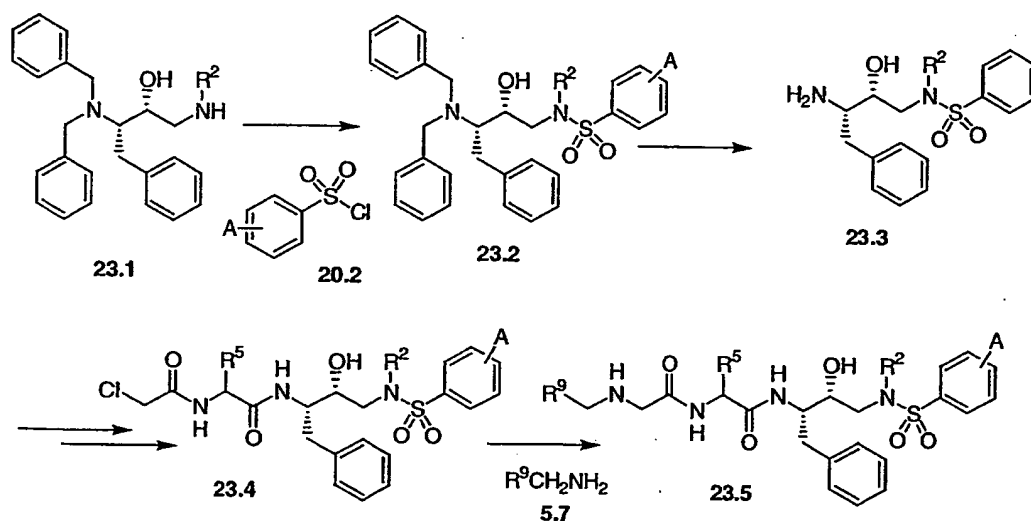**Scheme 20**

Scheme 21
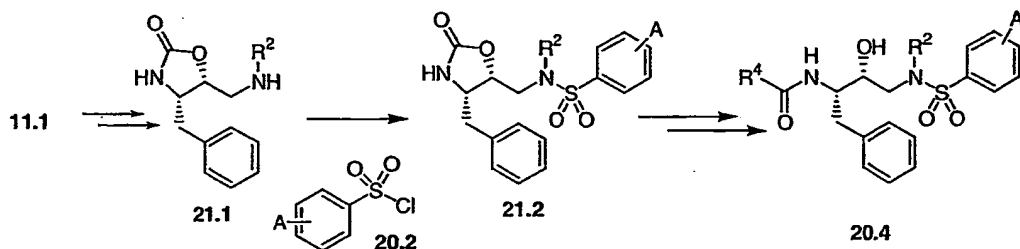
Scheme 22

Schemes **23** illustrates the preparation of the phosphonate esters **4** in which X is a direct bond and the R_4COOH group contains an amine group. The amine **23.1**, prepared from the epoxide

5   **13.1** and an amine **1.2** as described in Scheme **13** for the synthesis of **13.2** from **13.1**, is reacted with the sulfonyl chloride **20.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Schemes **1** for the synthesis of **1.5**, to give the product **23.2**. The product **23.2** is then reduced to amine **23.3** according to the conditions described in Scheme **3** for the preparation of **3.4** from **3.3**. The

10   amine product is then converted as described in Scheme **5** into the chloride **23.4**. The chloride is treated with the amine **5.7** to afford the amine **23.5**, as described in Scheme **5** for the preparation of **5.8** from **5.7**.
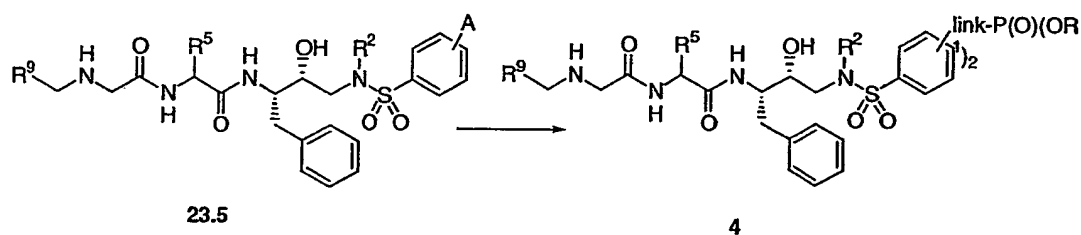
The reactions shown in Scheme 23 illustrate the preparation of the compound 23.5 in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 24 depicts the conversion of the compound 23.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 4 in which X is a direct bond. In this procedure, the compound 23.5 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

Scheme 23

23.1   20.2   23.2   23.3

23.4   R^{9}CH$_2$NH$_2$ 23.5
                      5.7

Scheme 24

23.5   4

Preparation of the phosphonate ester intermediates 4 in which X is a sulfur

The intermediate phosphonate ester 4, in which the group A is attached to a sulfur linked aryl moiety, and the R$_4$COOH group does not contain an amine is prepared as shown in Schemes 25-27. Amine 25.1 prepared from epoxide 15.1 and amine 1.2 as described in Scheme 15 is
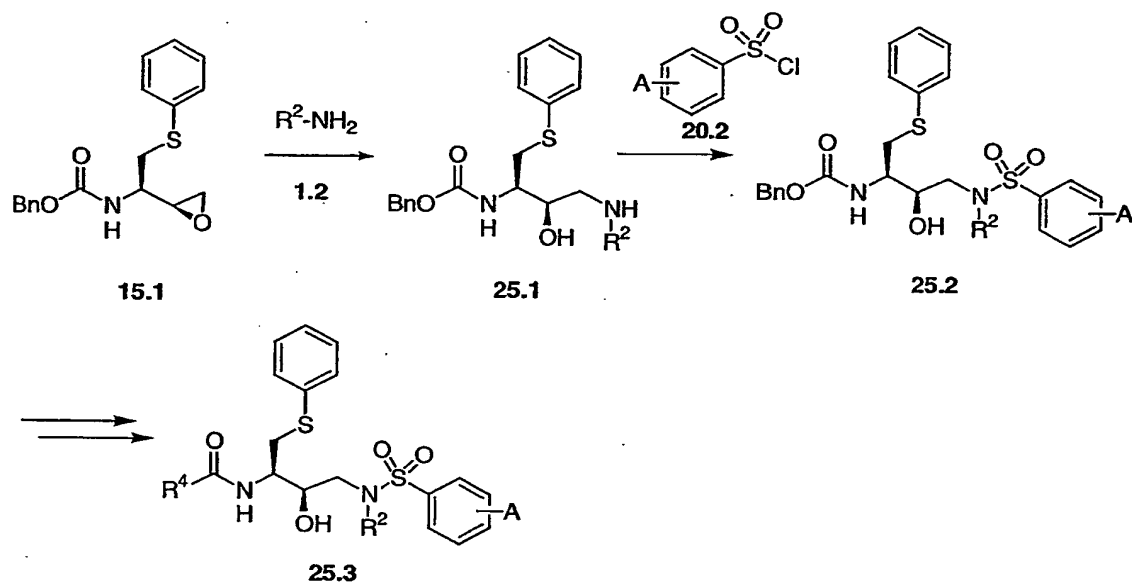
treated with sulfonamide **20.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described in Scheme **7**, to give the sulfonamide **25.2**. The sulfonamide **25.2** is then converted as described in Scheme **7** for the conversion of **7.9** to **7.10**, and Scheme **9a** for the conversion of **7.10** into **9a.4**, to the

5   product **25.3**. Alternatively, Scheme **26**, illustrates how the amine **8.5** prepared according to Scheme **8** is reacted with **20.2** under conditions described in Scheme **8** for the preparation of **8.6** from **8.5**, to give the sulfonamide **26.1**. Further modification according to the conditions described in Scheme **8** for the preparation of **7.11**, affords sulfonamide **25.3**.

10   The reactions shown in Scheme **25-26** illustrate the preparation of the compounds sulfonamide **25.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **27** depicts the conversion of **25.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **4** in which X is sulfur. In this procedure **25.3** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.
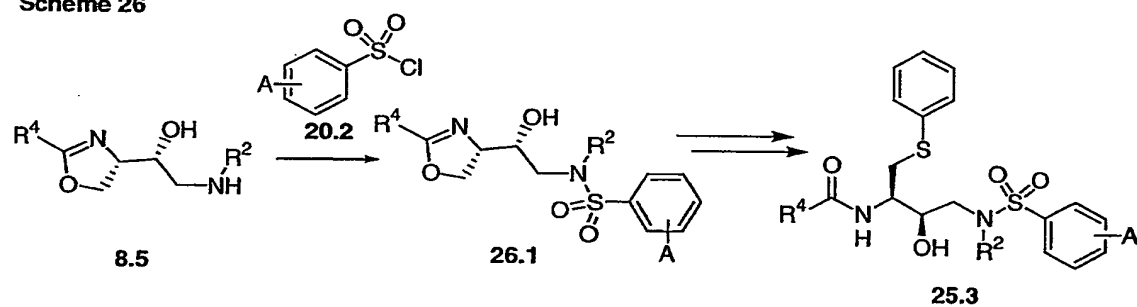
15

Preparation of the intermediate phosphonate ester **4**, in which the group A is attached to a sulfur linked aryl moiety, and the R$_4$COOH group contains an amine are prepared as shown in Schemes **28-29**. Amine **25.2** (Scheme **25**) in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, is converted to **28.1** as

20   described in Scheme **7** for the preparation of the amine **7.10** from **7.9** and Scheme **9a** for the preparation of **9a.4** from **7.10**.

The reactions shown in Scheme **28** illustrate the preparation of the compounds sulfonamide **28.1** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as

25   [OH], [SH], [NH], Br etc. Scheme **29** depicts the conversion of **28.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **4** in which X is sulfur. In this procedure **28.1** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.
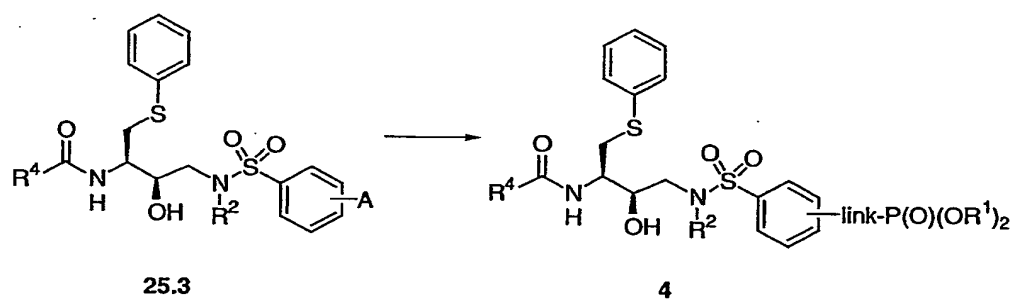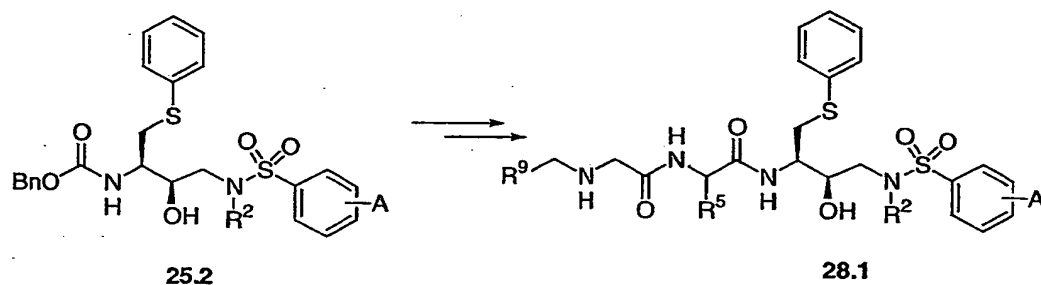
Scheme 25

15.1 → 25.1 → 25.2

25.3

Scheme 26

8.5 → 26.1 → 25.3

Scheme 27

25.3 → 4

Scheme 28
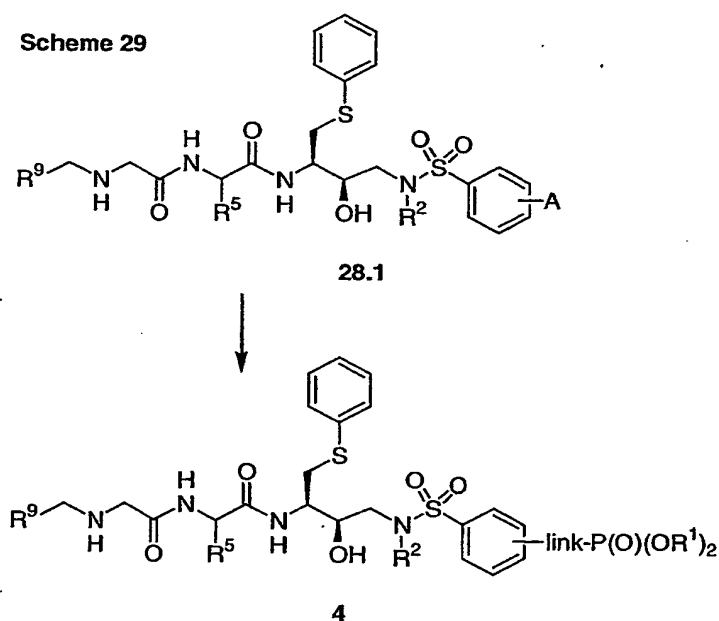

25.2   28.1

Scheme 29

28.1

4

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond

5   Schemes 30 illustrates the preparation of the phosphonate esters **5** in which X is a direct bond
and the R group does not contain a primary or secondary amine group. As shown in Scheme
30, the amine **23.1** (Scheme **23**) is reacted with the alcohol **30.1** in which the substituent A is
either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford
the carbamate **30.2**. The reaction is performed under conditions described below, Scheme 98,
10   for making carbamates from amines and alcohols. The preparation of the **30.1** is described in

Schemes 83-86. The carbamate 30.2 is then deprotected using conditions described in Scheme 3 for removal of the benzyl groups to give 30.3. Treatment of 30.3 with the R⁴COOH acid 1.7 using the conditions described in Scheme 1 then afford the amide 30.4
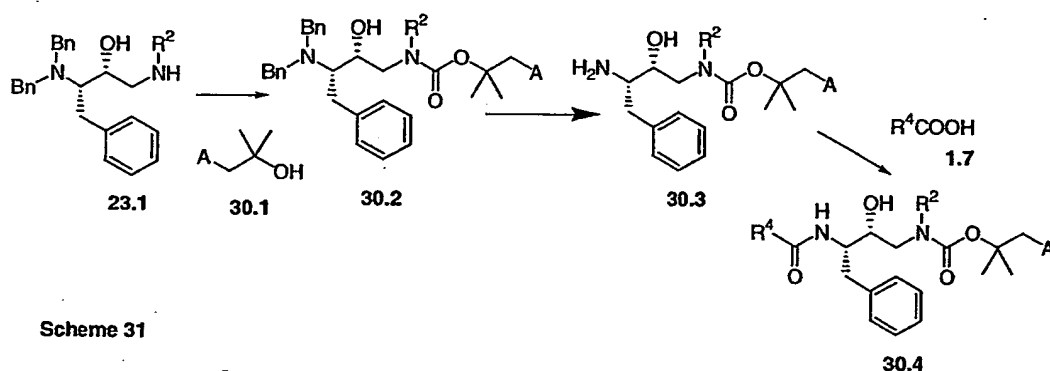
5 The reactions shown in Scheme 30 illustrate the preparation of the compound 30.4 in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 31 depicts the conversion of this compounds 30.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 5 respectively, in which X is a direct bond. In this procedure, the amines 30.4 is converted, using the procedures described below, Schemes 10 47-99, into the compounds 5.

Schemes 32 illustrates the preparation of the phosphonate esters 5 in which X is a direct bond and the R₄COOH group contains an amine. The carbamate 30.2 in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is 15 converted into the chloride 32.1 using conditions as described in Scheme 9a. Chloride 32.1 is then treated with amine 5.7 to give the amine 32.2, as described in Scheme 9a for the conversion of 7.10 into 9a.3.
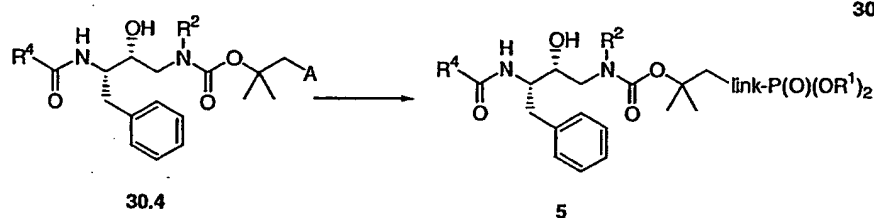
The reactions shown in Scheme 32 illustrate the preparation of the compound 32.2 in which 20 the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 33 depicts the conversion of the compound 32.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 5 in which X is a direct bond. In this procedure, the compound 32.2 is converted, using the procedures described below, Schemes 47-99, into the compound 5.
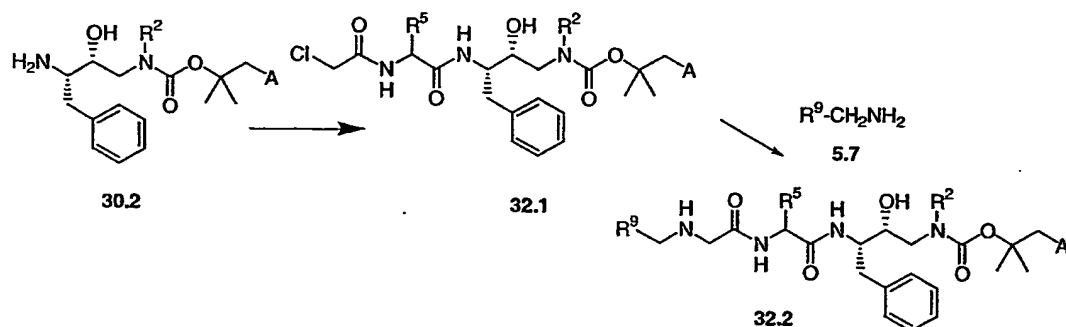
25

Scheme 30

Scheme 31
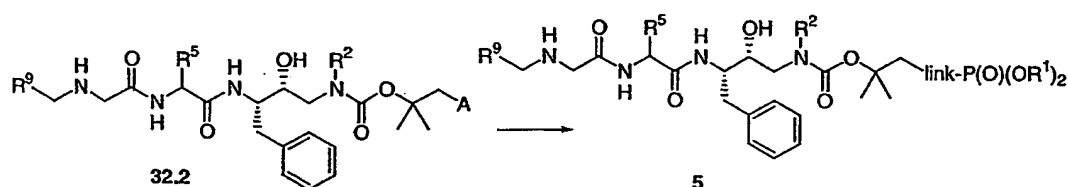
Scheme 32

Scheme 33

Preparation of the phosphonate ester intermediates 5 in which X is a sulfur

5   The intermediate phosphonate ester **5**, in which the group A is attached to a sulfur linked aryl moiety, is prepared as shown in Schemes **34-36**. Amine **25.1** prepared according to Scheme **25**, is treated with alcohol **30.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described below ,

Scheme 98, to give the carbamate **34.1**. The carbamate **34.1** is then converted as described in Scheme **7**, for the conversion of **7.9** to **7.11**, to the product **34.2**. Alternatively the amine **8.5** prepared according to Scheme **8** can be reacted with alcohol **30.1** under conditions described in Scheme **98** to give the carbamate **35.1**. Further modification according to the conditions

5   described in Scheme **8**, except incorporating thiophenol, then affords sulfonamide **34.2**.

The reactions shown in Scheme **34-35** illustrate the preparation of the compounds sulfonamide **34.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **36** depicts the conversion of **34.2** in which A is [OH],

10   [SH], [NH], Br etc, into the phosphonate **5** in which X is sulfur. In this procedure **34.2** is converted, using the procedures described below, Schemes **47-99**, into the compound **5**.
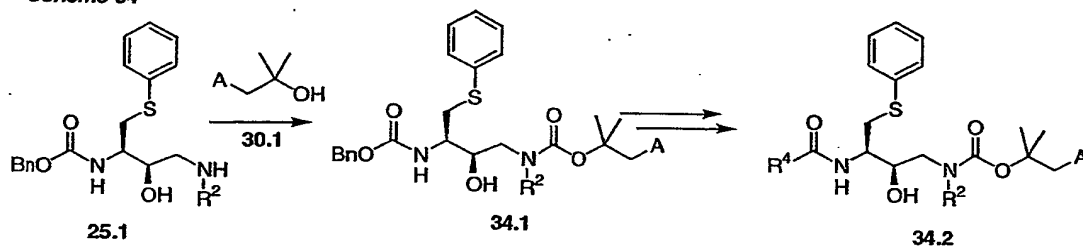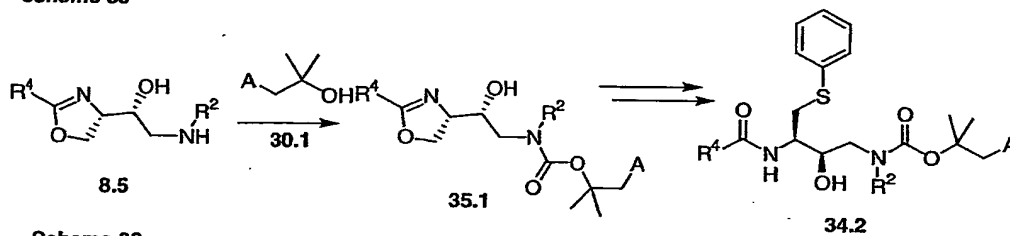
Preparation of the intermediate phosphonate ester **5**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains an amine are prepared as shown in

15   Schemes **37-38**. Carbamate **34.1** (Scheme **35**) in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is converted to **37.1**, as described in Scheme **7** for the preparation of the amine **7.10** from **7.9** and Scheme **9a** for the preparation of **9a.4** from **7.10**..

20   The reactions shown in Scheme **37** illustrate the preparation of the compounds sulfonamide **37.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **38** depicts the conversion of **37.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **5** in which X is sulfur. In this procedure **37.1** is converted, using the procedures described below, Schemes **47-99**, into the compound **5**.

25

Scheme 34

25.1   **34.1**   **34.2**

Scheme 35

8.5   **35.1**   **34.2**

Scheme 36

34.2   **5**

Scheme 37

34.1   **37.1**

Scheme 38

37.1

5
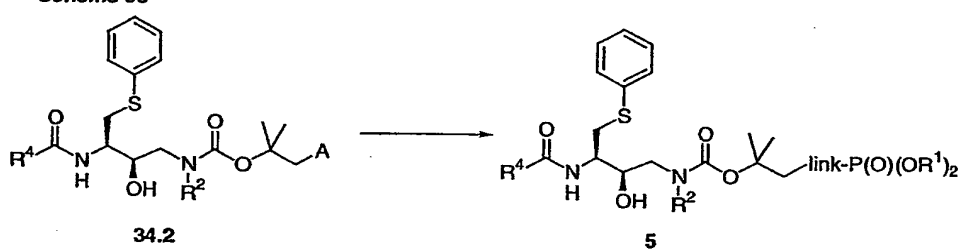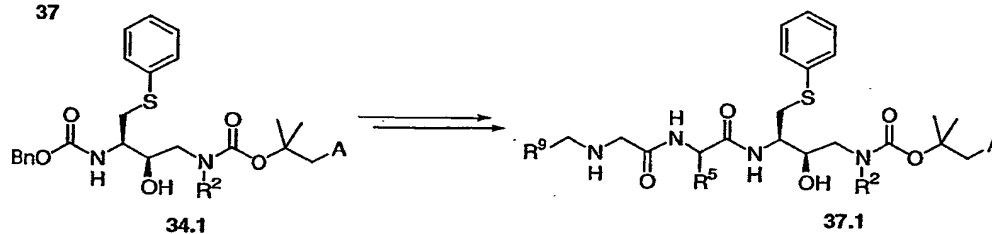
Preparation of the phosphonate ester intermediates 6 and 7 in which X is a direct bond

5   Schemes **39-40** illustrate the preparation of the phosphonate esters **6** and **7** in which X is a

direct bond. As shown in Scheme **39**, the epoxide **13.1**, prepared as described in Scheme **13** is

converted to the chloride **39.1**, as described in Scheme **3**, for the preparation of **3.4**, and

Scheme **5**, for the conversion of **3.4** into **5.6**. The chloride **39.1** is then reacted with the amine

39.2 or **39.4**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor

10   such as [OH], [SH], [NH], Br etc, to afford the amine **39.3** and **39.5** respectively. The reaction

is performed under the same conditions as described above, Scheme **5** for the preparation of

the amine **5.8** from **5.6**. The prepartion of **39.2** and **39.4**, amines in which A is link-

$P(O)(OR^1)_2$, are shown in Schemes **79-80** and Schemes **81-82** respectively.

15   The reactions shown in Scheme **39** illustrate the preparation of the compounds **39.3** and **39.5**

in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH],

[SH], [NH], Br etc. Scheme **40** depicts the conversion of these compounds **39.3** and **39.5** in

which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **6** and **7** respectively, in

which X is a direct bond. In this procedure, the amines **39.3** and **39.5** are converted, using the procedures described below, Schemes **47-99**, into the compounds **6** and **7** respectively.
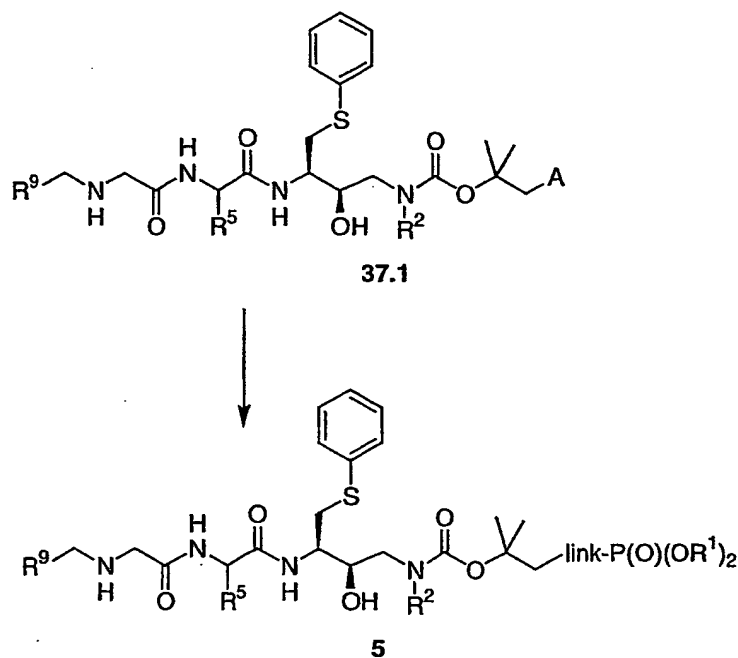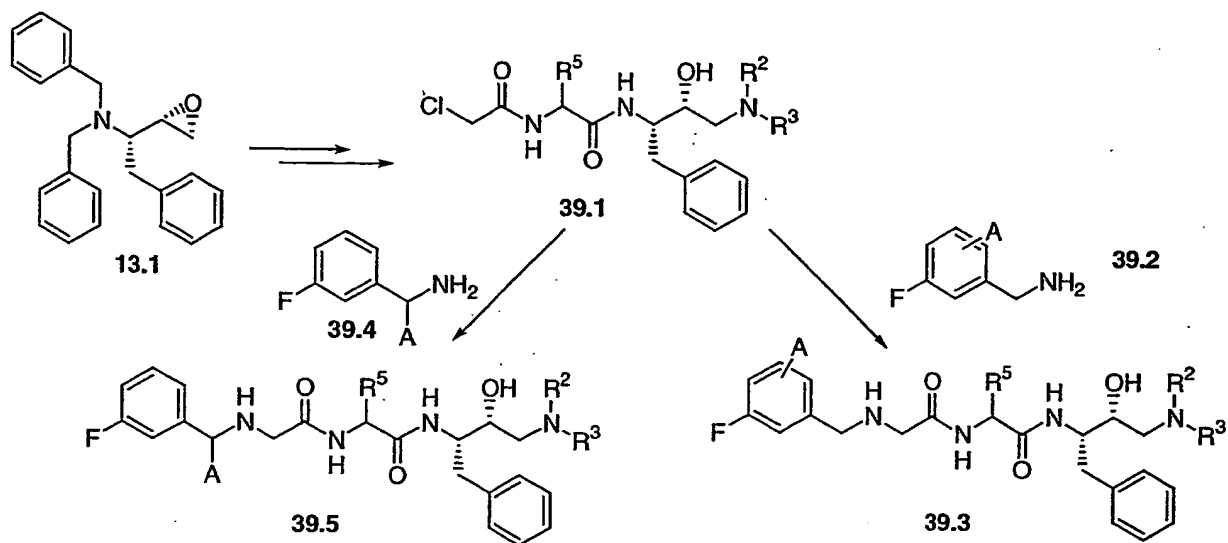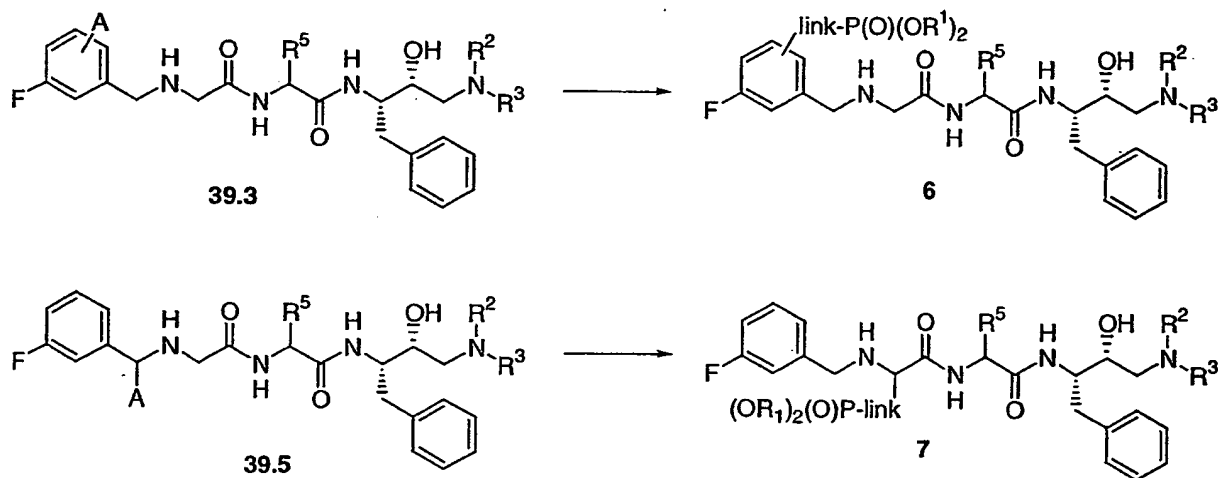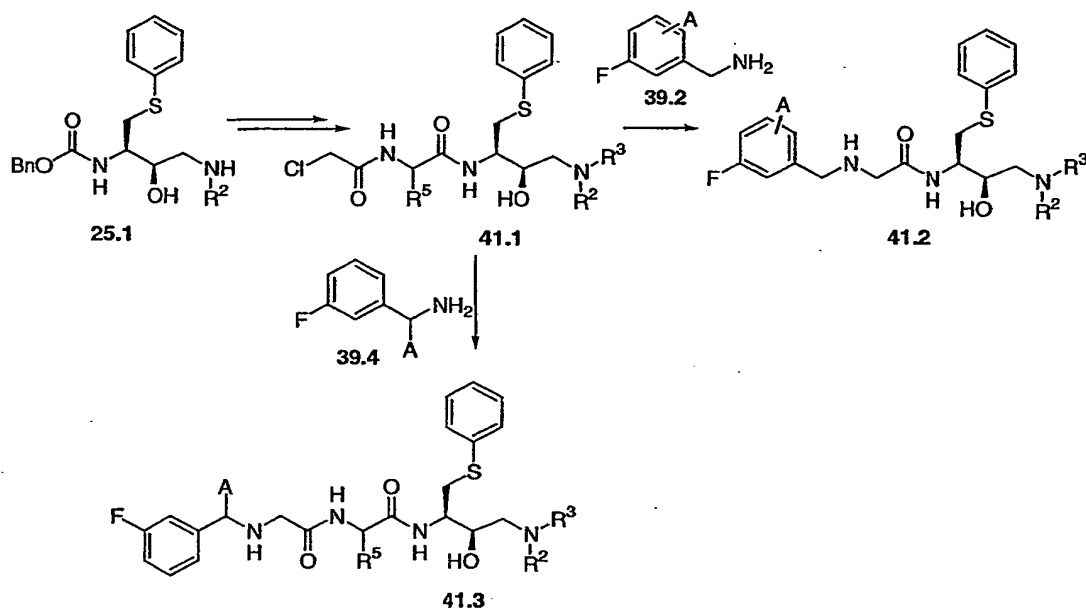
Scheme 39

Scheme 40

Preparation of the phosphonate ester intermediates 6 and 7 in which X is a sulfur

The intermediate phosphonate esters **6** and **7**, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Scheme **41-42**. The amine **25.1** (Scheme **25**) is

converted to the chloride **41.1** as described in Scheme **7** for the preparation of **7.10** from **7.8**, and Scheme **9a** for conversion of **7.10** to **9a3.** The chloride **41.1** is then treated with amine **39.2** or amine **39.4**, in which substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 5, to give the amines **41.2** and **41.3**

5   respectively.

The reactions shown in Scheme **41** illustrate the preparation of the compounds **41.2** and **41.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **42** depicts the conversion of **41.2** and **41.3** in which A is [OH],

10   [SH], [NH], Br etc, into the phosphonate ester **6** and **7** in which X is sulfur. In this procedure **41.2** or **41.3** is converted, using the procedures described below, Schemes 47-99, into the compound **6** and **7**.

Scheme 41

Scheme 42
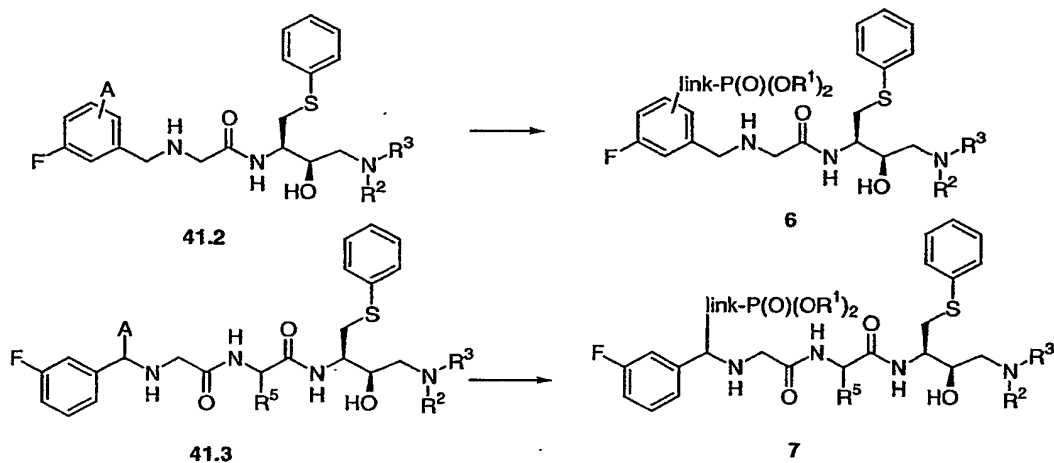
Preparation of the phosphonate ester intermediates 8-10 in which X is a direct bond

5   Schemes **43-44** illustrate the preparation of the phosphonate esters **8-10** in which X is a direct
bond. As shown in Scheme **43**, the amine **43.1** prepared from **10.1** or **21.2** is reacted with the
acid **43.2**, **43.4** or **43.6**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a
precursor such as [OH], [SH], [NH], Br etc, to afford the amide **43.3**, **43.5** and **43.7**
respectively. The reaction is performed under the same conditions as described above, Scheme

- 940 -

1 for the preparation of the amide **1.8**. Amine **43.1** is prepared from epoxide **10.1** using the
conditions described in Scheme **1** except utilising **10.1** in place of **1.1**. Amine **43.1** is prepared
from **21.2** according to the conditions described in Scheme **2** except utilizing **21.2** in place of
2.1. The preparation of the acid **43.2** is described in Schemes **47-51**, acid **43.4** is described in

5   Schemes **87-91**, and acid **43.6** is described in Schemes **52-55**.

The reactions shown in Scheme **43** illustrate the preparation of the compounds **43.3**, **43.5** and
43.7 in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as
[OH], [SH], [NH], Br etc. Scheme **44** depicts the conversion of these compounds **43.3**, **43.5**,

10   and **43.7** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **8**, **9** and **10**
respectively, in which X is a direct bond. In this procedure, the amines **43.3**, **43.5** and **43.7** are
converted, using the procedures described below, Schemes **47-99**, into the compounds **8**, **9**,
and **10** respectively.

Scheme 43

15

Scheme 44

43.3 ⟶ 8

43.5 ⟶ 9

43.7 ⟶ 10
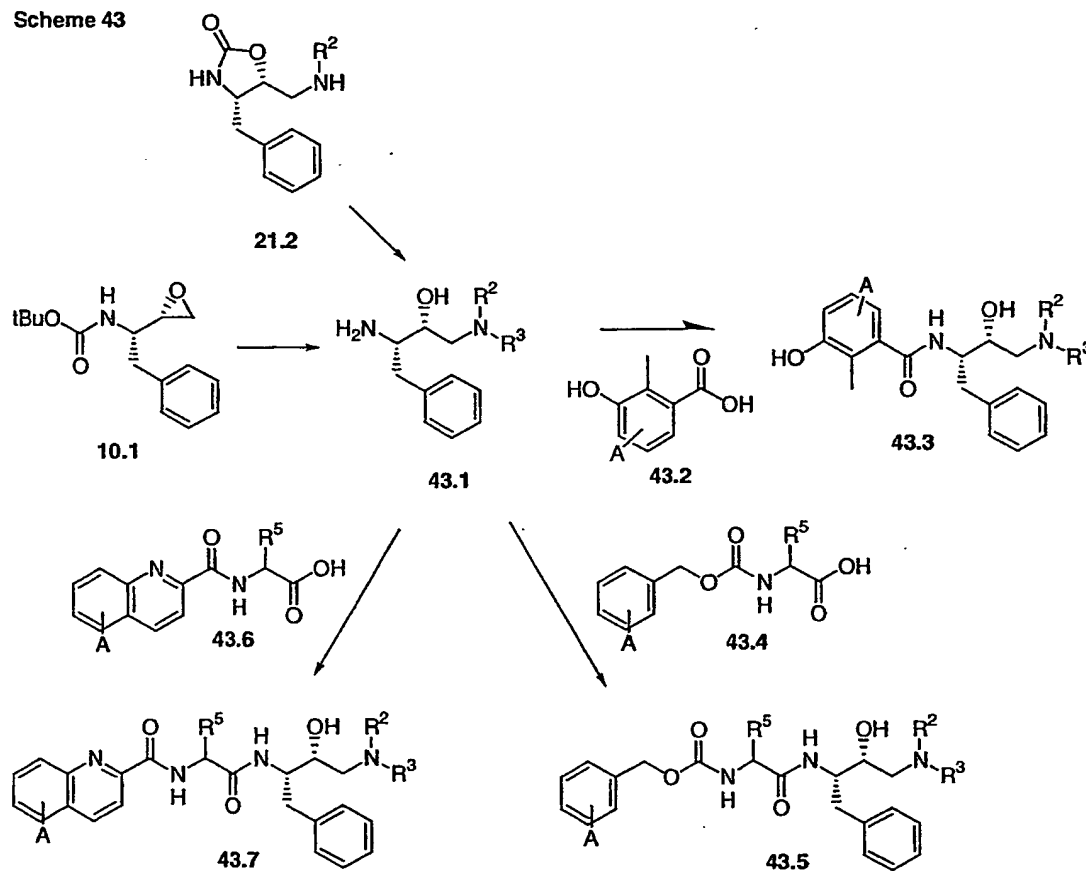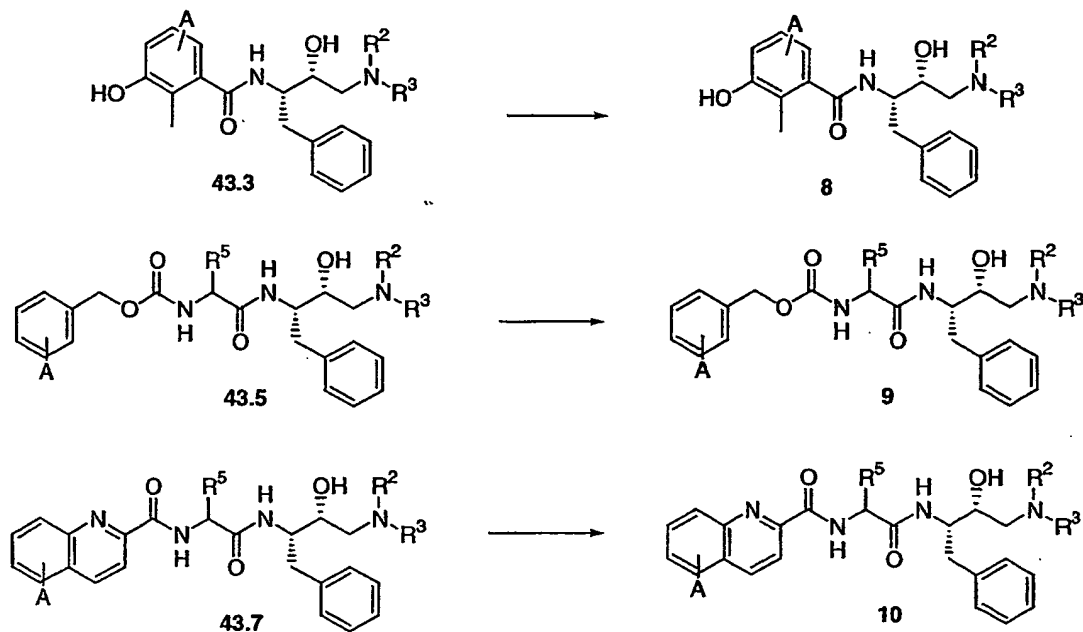
Preparation of the phosphonate ester intermediates 8-10 in which X is a sulfur

5   The intermediate phosphonate esters **8-10**, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Schemes **45-46**. In Scheme **45**, epoxide **15.1** is prepared from mesylate **7.1** using the conditions described in Scheme **7** except incorporating thiophenol for thiol **7.2**. The epoxide **15.1** is then converted to amine **45.1** according to the conditions described in Scheme **7** for the preparation of **7.10** from **7.7**. Amine **45.1** is then

10   treated with acids **43.2**, **43.4** or **43.6**, in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **7**, to give the amides **45.2**, **45.3**, and **45.4** respectively.

The reactions shown in Scheme **45** illustrate the preparation of the compounds **45.2**, **45.3**, and

15   **45.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **46** depicts the conversion **45.2**, **45.3**, and **45.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **8, 9** and **10** respectively in which X is sulfur. In this procedure **45.2**, **45.3**, and **45.4** is converted, using the procedures described below, Schemes **47-99**, into the compounds **8, 9** and **10** respectively.

Scheme 45
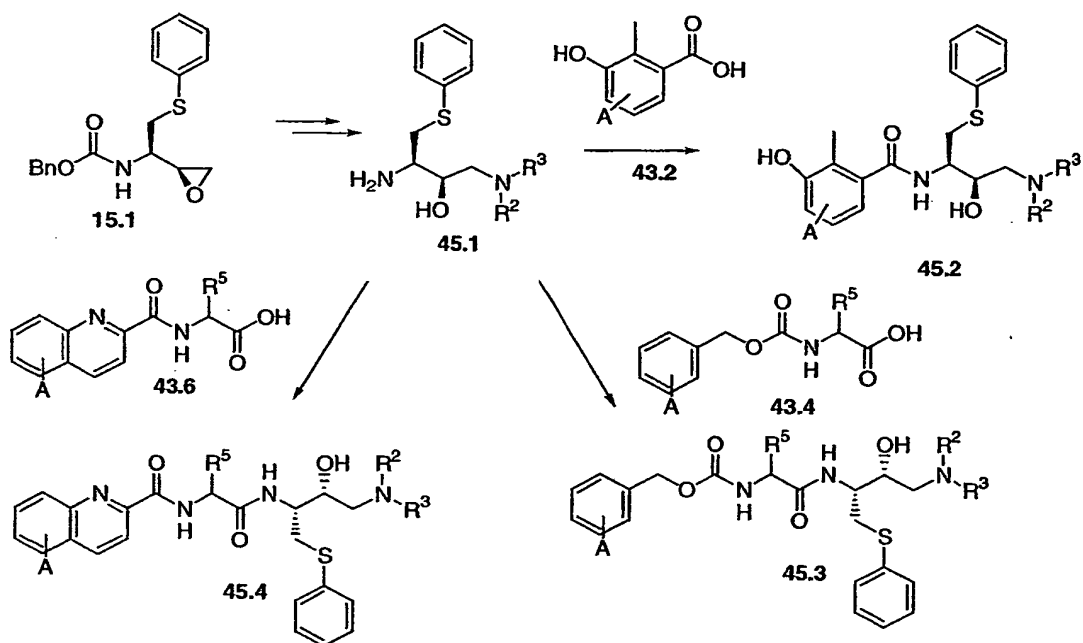
Scheme 46
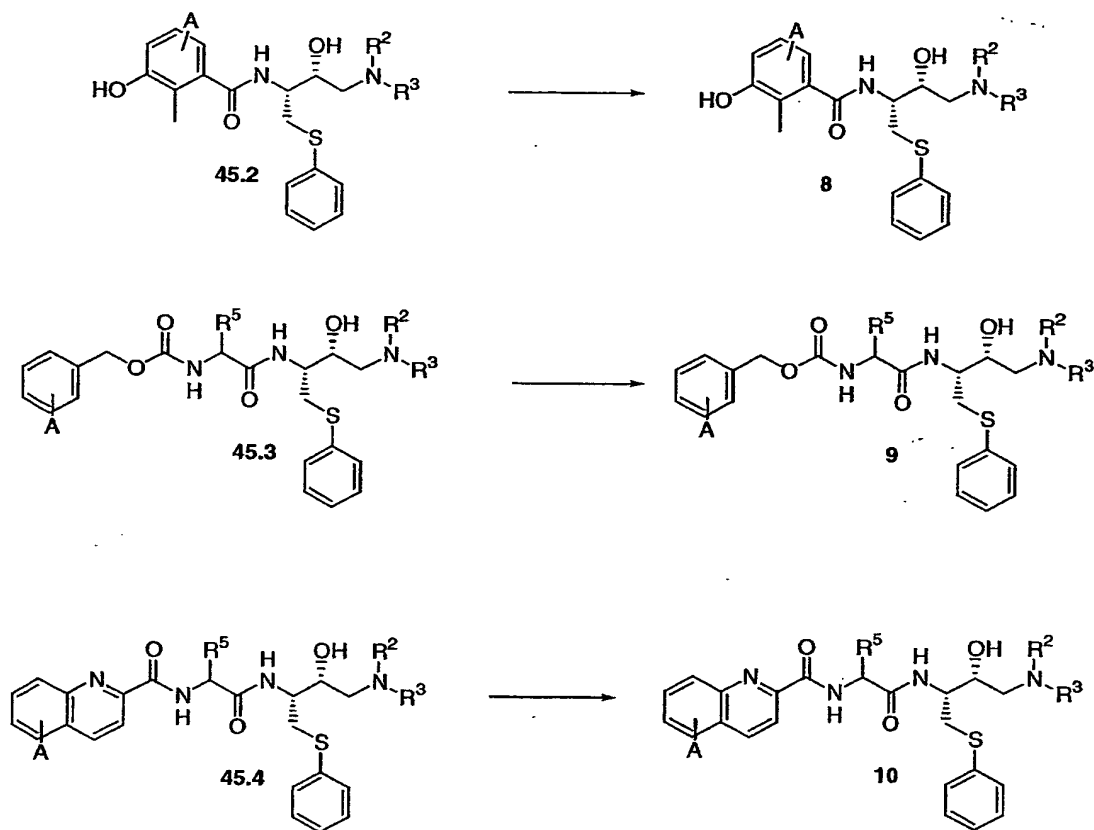
Preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2.

5   Schemes 47 - 51 illustrate methods for the preparation of phosphonate-containing
hydroxymethyl benzoic acids **43.2** which are employed in the preparation of the phosphonate
esters **8**.

Scheme **47** illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in
which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably

10   protected bromo hydroxy methyl benzoic acid **47.1** is subjected to halogen-methyl exchange to
afford the organometallic intermediate **47.2**. This compound is reacted with a chlorodialkyl
phosphite **47.3** to yield the phenylphosphonate ester **47.4**, which upon deprotection affords the
carboxylic acid **47.5**.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **47.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **47.7**, as described in

5   Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **47.8**. This compound is treated with boron trifluoride at 0^0 to effect rearrangement to the orthoester **47.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **47.10**. Halogen-metal exchange is performed by the

10   reaction of the substrate **47.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **47.3**, to produce the phosphonate **47.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **47.12**.

15   Using the above procedures, but employing, in place of the bromo compound **47.6**, different bromo compounds **47.1**, there are obtained the corresponding products **47.5**.

Scheme **48** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

20   In this method, a suitably protected dimethyl hydroxybenzoic acid, **48.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **48.2** is reacted with a sodium dialkyl phosphite, **48.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **48.4**. Deprotection of the carboxyl function then yields the carboxylic acid **48.5**.

25   For example, 2,5-dimethyl-3-hydroxybenzoic acid, **48.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **48.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or

30   diisopropylethylamine. The product **48.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **48.8**. This compound is then reacted with a sodium dialkyl

phosphite **48.3** in tetrahydrofuran, as described above, to afford the phosphonate **48.9**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **48.10**. Using the above procedures, but employing, in place of the methyl compound **48.6**, different

5   methyl compounds **48.1**, there are obtained the corresponding products **48.5**.

Scheme **49** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.
In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic

10   acid **49.1** is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **49.2**, to afford the coupled product **49.3**, which upon deprotection affords the carboxylic acid **49.4**.
For example, 3,6-dihydroxy-2-methylbenzoic acid, **49.5**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **49.6**, by

15   treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether **49.7**. This compound is then reacted

20   with a dialkyl hydroxymethylphosphonate **49.2**, under the conditions of the Mitsonobu reaction. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in

25   an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the coupled product **49.8**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic

30   carboxylic acid **49.9**.
Using the above procedures, but employing, in place of the phenol **49.5**, different phenols or thiophenols **49.1**, there are obtained the corresponding products **49.4**.

Scheme **50** depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate **50.2** is coupled, by means of a palladium

5 catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **50.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a

10 palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product **50.3** is deprotected to afford the phosphonate **50.4**; the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid **50.5**.

15 For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **50.6**, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **50.7** as described above. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **50.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above to afford the product **50.9**. Deprotection, or hydrogenation/deprotection, of

20 this compound, as described above, then affords respectively the unsaturated and saturated products **50.10** and **50.11**.

Using the above procedures, but employing, in place of the bromo compound **50.6**, different bromo compounds **50.1**, and/or different phosphonates **50.2**, there are obtained the corresponding products **50.4** and **50.5**.

25

Scheme **51** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **51.1** is converted to the corresponding boronic acid **51.2**, by metallation with butyllithium and

30 boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate **51.3**. The product **51.4** is then deprotected to afford the diaryl phosphonate product **51.5**.

For example, the silylated OBO ester **51.6**, prepared as described above, (Scheme **47**), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp. Radiopharm., 1992, 31, 175, is converted into the boronic acid **51.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **51.8**, prepared as described in

5   J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **51.9**. Deprotection, as described above, then affords the benzoic acid **51.10**.
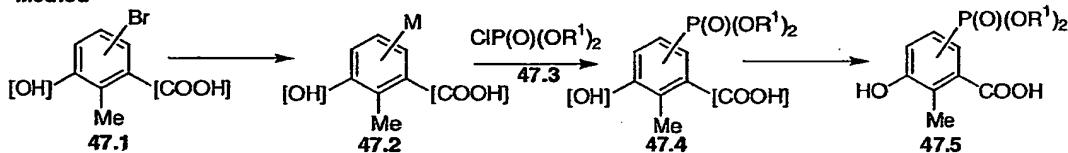
Using the above procedures, but employing, in place of the bromo compound **51.6**, different
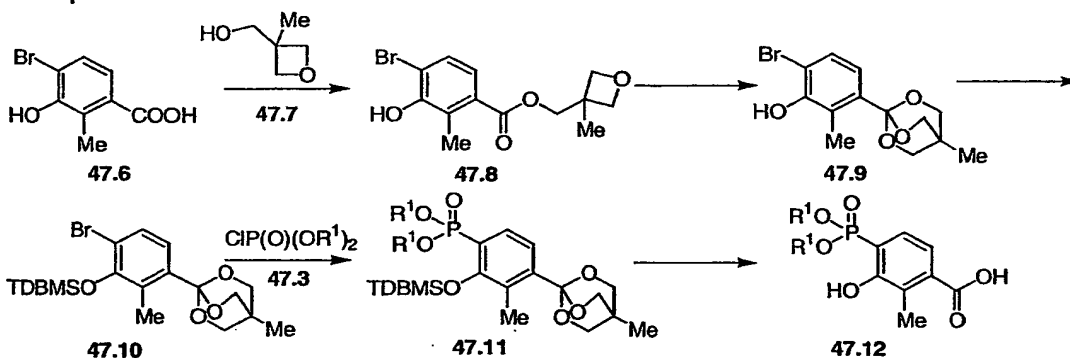
10   bromo compounds **51.1**, and/or different phosphonates **51.3**, there are obtained the corresponding carboxylic acid products **51.5**.

Scheme 47

Method

Example

Scheme 48
Method

48.1   →   48.2   →(NaP(O)(OR¹)₂, 48.3)→   48.4   →   48.5

Example

48.6   →   48.7 MOM = CH₃OCH₂O   →   48.8   →(NaP(O)(OR¹)₂, 48.3)→   48.9

48.10

Scheme 49
Method

49.1
X = O, S
→(HOCH₂P(O)(OR¹)₂, 49.2)→   49.3   →   49.4

Example

49.5   →   49.6   →   49.7   →(HOCH₂P(O)(OR¹)₂, 49.2)→

49.8   →   49.9
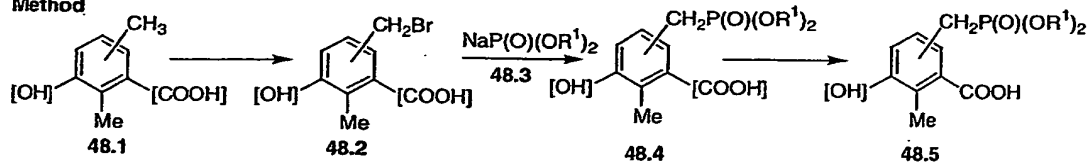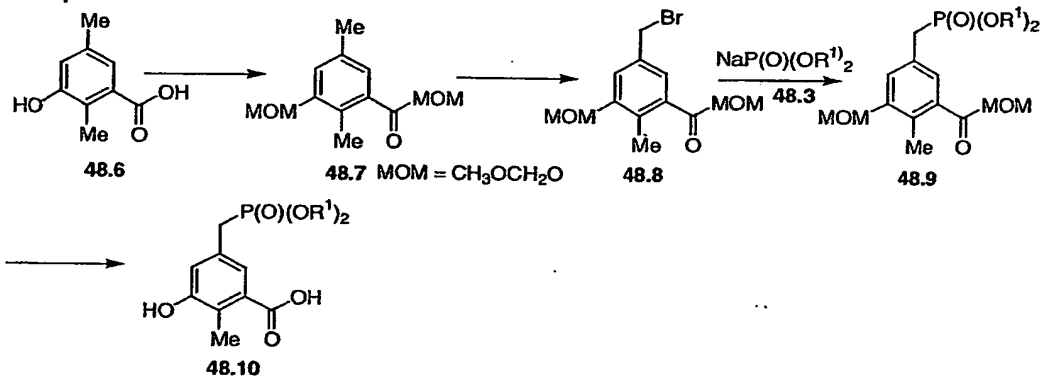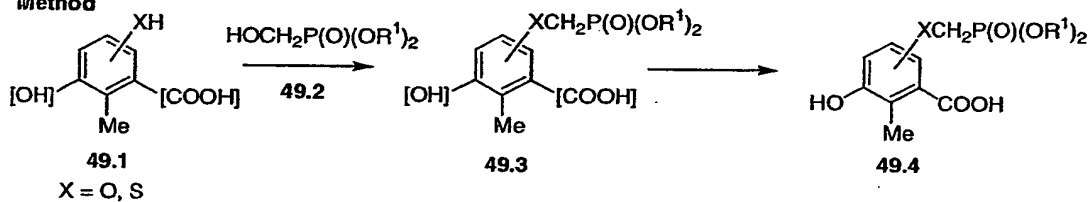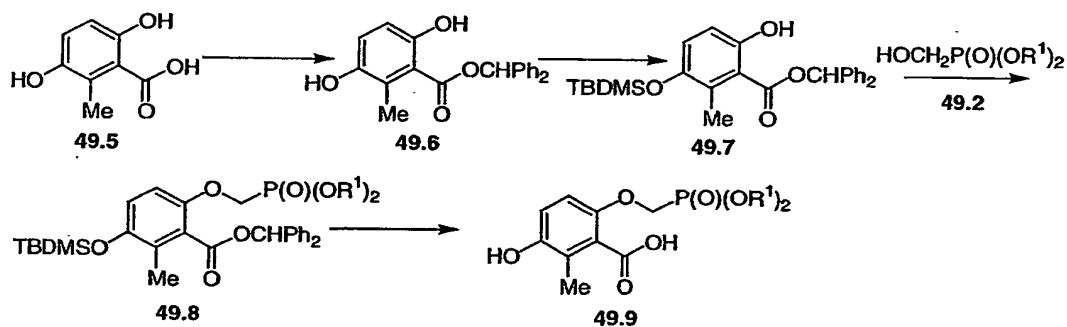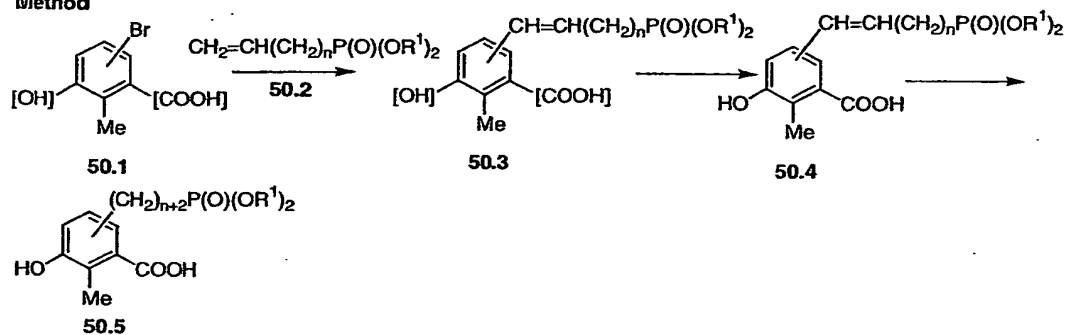
Scheme 50
Method

Example

Scheme 51
Method

Example

Preparation of quinoline 2-carboxylic acids 43.6 incorporating phosphonate moieties.

The reaction sequences depicted in Schemes **43 - 46** for the preparation of the phosphonate
5   esters **10** employ a quinoline-2-carboxylic acid reactant **43.6** in which the substituent A is
either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc.
A number of suitably substituted quinoline-2-carboxylic acids are available commercially or
are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino
and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het.
10   Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the
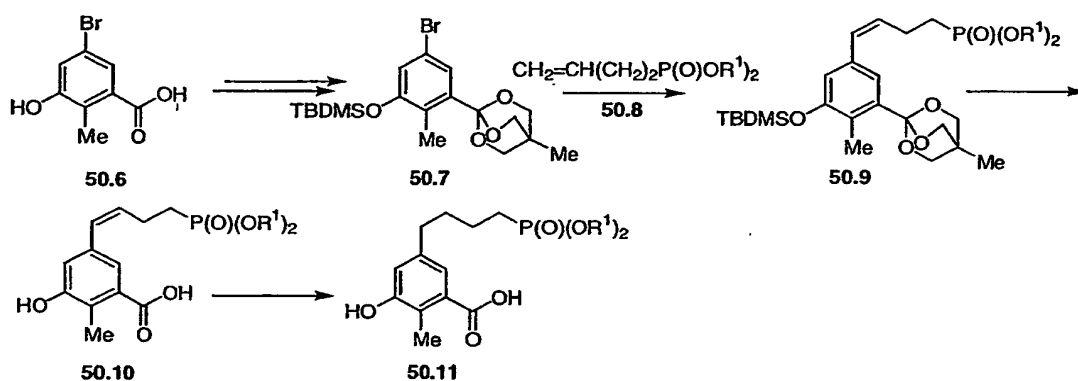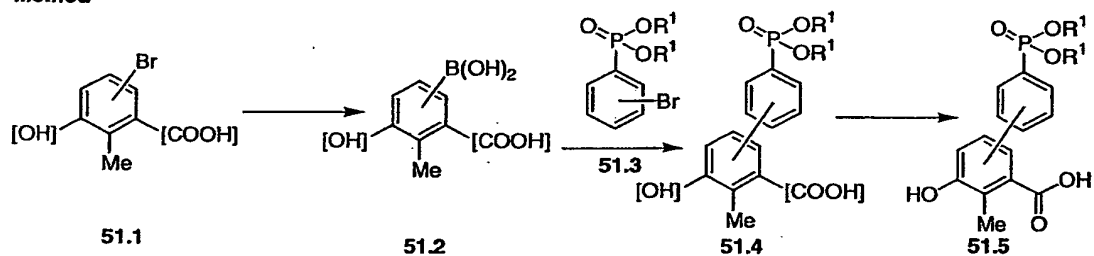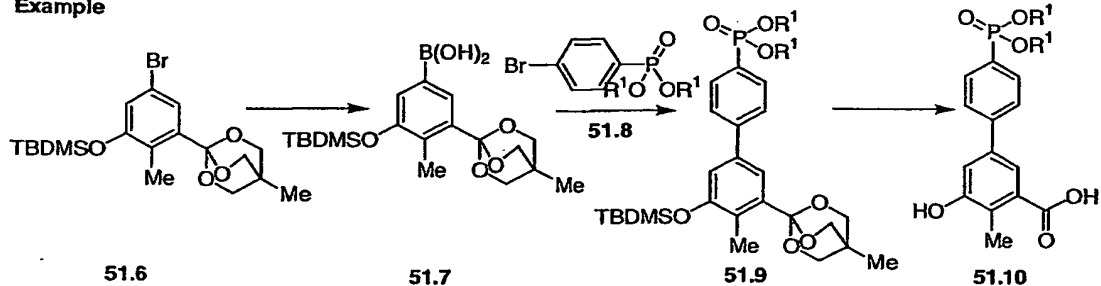preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987,
109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures
known to those skilled in the art. The synthesis of variously substituted quinolines is described,
for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p
15   93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction,
which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed.,
Wiley, 1952, p. 204.

Scheme **52** illustrates the preparation of quinoline-2-carboxylic acids by means of the
20   Friedlander reaction, and further transformations of the products obtained. In this reaction
sequence, a substituted 2-aminobenzaldehyde **52.1** is reacted with an alkyl pyruvate ester **52.2**,
in the presence of an organic or inorganic base, to afford the substituted quinoline-2-
carboxylic ester **52.3**. Hydrolysis of the ester, for example by the use of aqueous base, then
afford the corresponding carboxylic acid **52.4**. The carboxylic acid product **52.4** in which X is
25   NH_2 can be further transformed into the corresponding compounds **52.6** in which Z is OH, SH
or Br. The latter transformations are effected by means of a diazotization reaction. The
conversion of aromatic amines into the corresponding phenols and bromides by means of a
diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner,
H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding
30   thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the
diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium
tetrafluoborate, is then heated in aqueous solution, for example as described in Organic

Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to

afford the corresponding phenol 52.6, Y = OH. Alternatively, the diazonium salt is reacted in

aqueous solution with cuprous bromide and lithium bromide, as described in Organic

Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138,

5   to yield the corresponding bromo compound, 52.6, Y = Br. Alternatively, the diazonium

tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as

described in Sulfur Lett., 2000, 24, 123, to afford the thiol 52.6, Y = SH. Optionally, the

diazotization reactions described above can be performed on the carboxylic esters 52.3 instead

of the carboxylic acids 52.5.

10   For example, 2,4-diaminobenzaldehyde 52.7 (Apin Chemicals) is reacted with one molar

equivalent of methyl pyruvate 52.2 in methanol, in the presence of a base such as piperidine, to

afford methyl-7-aminoquinoline-2-carboxylate 52.8. Basic hydrolysis of the product,

employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the

carboxylic acid 52.9. The amino-substituted carboxylic acid is then converted into the

15   diazonium tetrafluoborate 52.10 by reaction with sodium nitrite and tetrafluoboric acid. The

diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic

acid, 52.11, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic

solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-

bromoquinoline-2-carboxylic acid 52.11, Z = Br. Alternatively, the diazonium tetrafluoborate

20   52.10 is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as

described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid

52.11, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde 52.7,

different aminobenzaldehydes 52.1, the corresponding amino, hydroxy, bromo or mercapto-

25   substituted quinoline-2-carboxylic acids 52.6 are obtained. The variously substituted quinoline

carboxylic acids and esters can then be transformed, as described herein, (Schemes 53 – 55)

into phosphonate-containing derivatives.

Scheme 53 depicts the preparation of quinoline-2-carboxylic acids incorporating a

30   phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In

this procedure, an amino-substituted quinoline-2-carboxylate ester 53.1 is transformed, via a

diazotization procedure as described above (Scheme 52) into the corresponding phenol or

thiol **53.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate

53.3, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **53.4**.

The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for

example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448,

5   and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001,

p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an

aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl

azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **53.4**. Basic

hydrolysis of the ester group, for example employing one molar equivalent of lithium

10 hydroxide in aqueous methanol, then yields the carboxylic acid **53.5**. The product is then

coupled with a suitably protected aminoacid derivative **53.6** to afford the amide **53.7**. The

reaction is performed under similar conditions to those described above, Scheme **1**. The ester

protecting group is then removed to yield the carboxylic acid **53.8**.

For example, methyl 6-amino-2-quinoline carboxylate **53.9**, prepared as described in J. Het.

15 Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above,

into methyl 6-mercaptoquinoline-2-carboxylate **53.10**. This material is reacted with a dialkyl

hydroxymethylphosphonate **53.11** (Aldrich) in the presence of diethyl azodicarboxylate and

triphenylphosphine in tetrahydrofuran solution, to afford the thioether **53.12**. Basic hydrolysis

then afford the carboxylic acid **53.13**. The latter compound is then converted, as described

20 above, into the aminoacid derivative **53.16**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline

carboxylate **53.9**, different aminoquinoline carboxylic esters **53.1**, and/or different dialkyl

hydroxymethylphosphonates **53.3** the corresponding phosphonate ester products **53.8** are

obtained.

25

Scheme **54** illustrates the preparation of quinoline-2-carboxylic acids incorporating

phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated

carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **54.1** is

coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate

30 **54.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for

example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001,

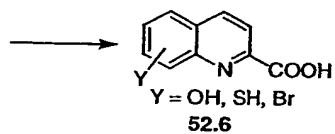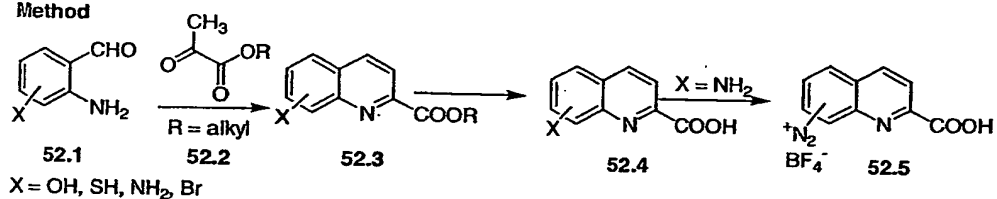p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as

dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as .

tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II)

acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate.

Thus, Heck coupling of the bromo compound **54.1** and the olefin **54.2** affords the olefinic

5   ester **54.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or

by treatment with porcine liver esterase, then yields the carboxylic acid **54.4**. The latter

compound is then transformed, as described above, into the homolog **54.5**. Optionally, the

unsaturated carboxylic acid **54.4** can be reduced to afford the saturated analog **54.6**. The

reduction reaction can be effected chemically, for example by the use of diimide or diborane,

10   as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5,

or catalytically. The product **54.6** is then converted, as described above (Scheme 53) into the

aminoacid derivative **54.7**.

For example, methyl 7-bromoquinoline-2-carboxylate, **54.8**, prepared as described in J.

Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a

15   dialkyl vinylphosphonate **54.9** (Aldrich) in the presence of 2 mol% of

tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **54.10**

The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the

carboxylic acid **54.11**. The latter compound is reacted with diimide, prepared by basic

hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965,

20   to yield the saturated product **54.12**. The latter compound is then converted, as described

above, into the aminoacid derivative **54.13**. The unsaturated product **54.11** is similarly

converted into the analog **54.14**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-

quinolinecarboxylate **54.8**, different bromoquinoline carboxylic esters **54.1**, and/or different

25   dialkyl alkenylphosphonates **54.2**, the corresponding phosphonate ester products **54.5** and

54.7 are obtained.

Scheme 52

Method

52.1   **52.2**   **52.3**   **52.4**   **52.5**

X = OH, SH, NH₂, Br

Y = OH, SH, Br
52.6

Example

52.7   **52.2**   **52.8**   **52.9**   **52.10**

Z = OH, SH, Br
52.11

Scheme 53
Method

53.1   53.2   X = O, S   53.3   53.4

53.5   53.6   53.7

53.8

Example

53.9   53.10   53.11   53.12

53.13   53.14   53.15

53.16
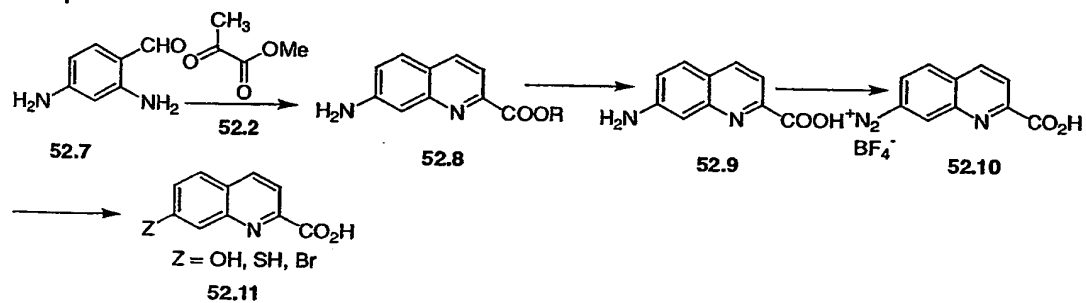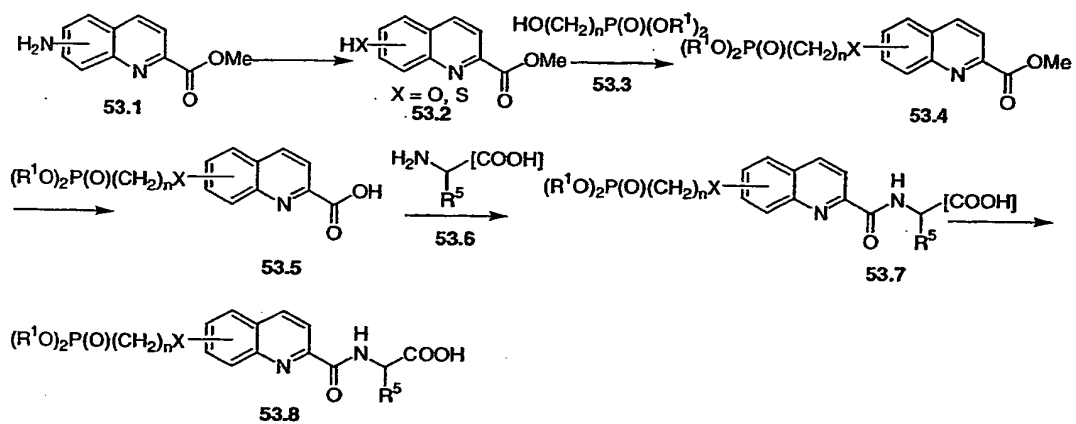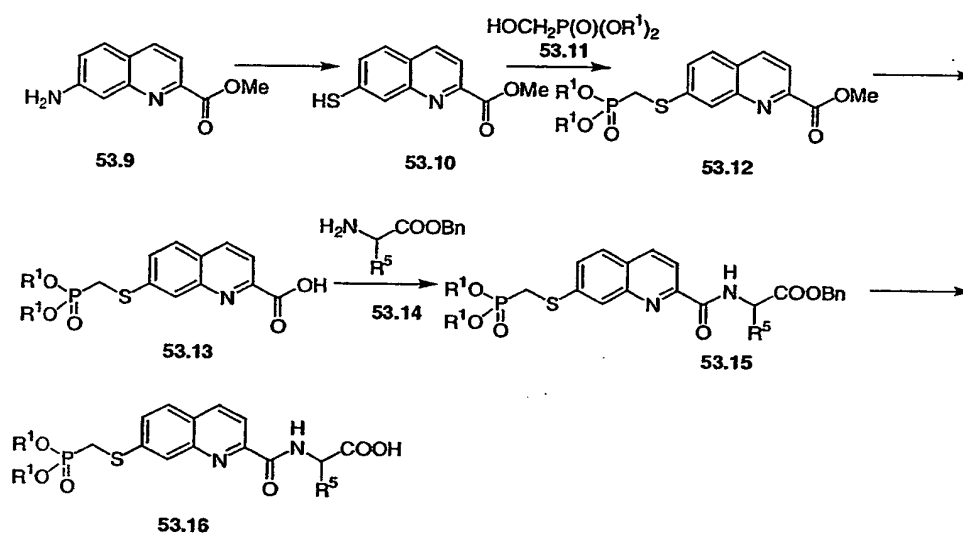
Scheme 54

Method

Example

Scheme 55 depicts the preparation of quinoline-2-carboxylic acid derivatives **55.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this

5   reaction sequence, a methyl aminoquinoline-2-carboxylate **55.1** is reacted with a phosphonate aldehyde **55.2** under reductive amination conditions, to afford the aminoalkyl product **55.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p

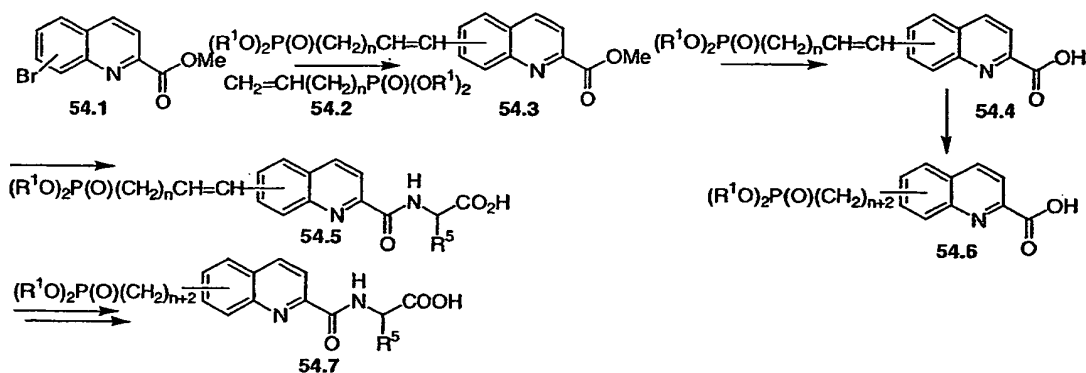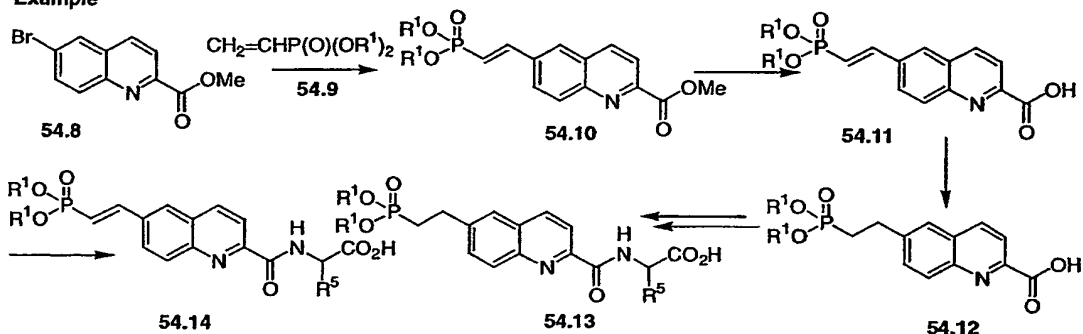10   269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **55.3** is then hydrolyzed to yield the free carboxylic

15   acid **55.4**. The latter compound is then converted, as described above, into the aminoacid derivative **55.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **55.6**, prepared as described in J. Am. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **55.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **55.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **55.9**. The latter compound is then converted, as described above, into the aminoacid derivative **55.10**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **55.7**, different formylalkyl phosphonates **55.2**, and/or different aminoquinolines **55.1**, the corresponding products **55.5** are obtained.

Scheme 55

Method
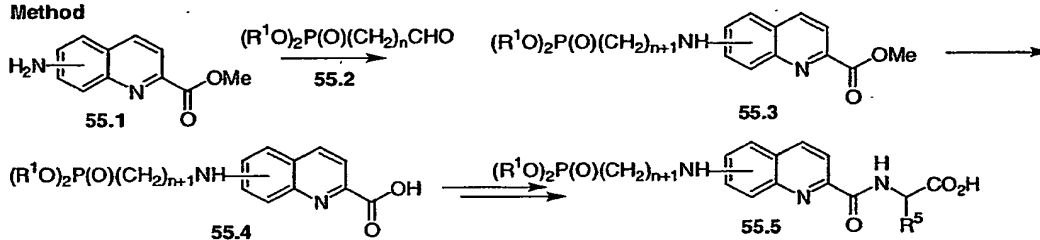
Example
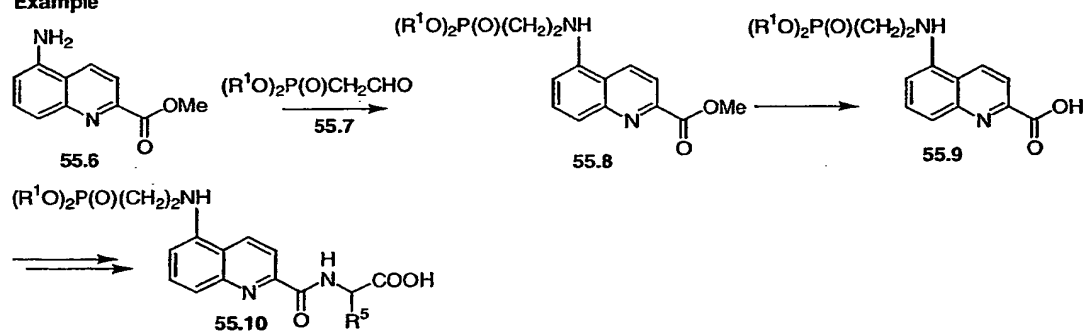
Preparation of phenylalanine derivatives 1.1 incorporating phosphonate moieties.

Scheme **56** illustrates the conversion of variously substituted phenylalanine derivatives **56.1** into epoxides **1.1**, the incorporation of which into the compounds **1** is depicted in Schemes **1** and **3**.

A number of compounds **56.1** or **56.2**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH$_2$ are commercially available. The preparations of different compounds **56.1** or **56.2** are described in the literature. For example, the preparation of compounds **56.1** or **56.2** in which

X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Am. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds 56.1, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth.
5   Org. Chem., 1992, 2, 35.

The variously substituted aminoacids 56.2 are protected, for example by conversion to the BOC derivative 56.3, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product 56.3 is then converted into the methyl ester 56.4, for example by treatment with ethereal diazomethane. The substituent X in 56.4 is then transformed, using the
10   methods described below, Schemes 57-59, into the group A. The products 56.5 are then converted, via the intermediates 56.6 - 56.9, into the epoxides 1.1. The methyl ester 56.5 is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid 56.6. The conversion of the carboxylic acid 56.6 into the epoxide
15   1.1, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 56.7. The diazoketone is converted into
20   the chloroketone 56.8 by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer 56.9 is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide 1.1. Optionally, the above
25   described series of reactions can be performed on the methyl ester 56.4, so as to yield the epoxide 1.1 in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds 56.4, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes 57-59.

30   Scheme 56a illustrates the conversion of variously substituted phenylalanine derivatives 56a.1 into epoxides 3.1, the incorporation of which into the compounds 1 is depicted in Schemes 3. Starting from the same reagents described above, Scheme 56, the compound 56.2 is converted

into the epoxide **56a.6** as described in J. Org. Chem 1996,61, 3635. The amino acid **56.2** is converted to the tribenzyl ester **56a.3** by treatment with benzyl bromide in ethanol in the presence of potassium carbonate. The substituent X in **56a.3** is then transformed, using the methods described below, Schemes **57-59**, into the group A, compound **56a.4**. These

5   methods describe procedures in which the amine is BOC protected. However the same procedures are applicable to other amine protecting groups such as dibenzyl. The products **56a.4** are then converted, via the intermediates **56a.5** into the epoxides **3.1**. The ester **56a.4** is reduced with lithium aluminum hydride to the alcohol which is then oxidized to the aldehyde **56a.4** by treatment with pyridine sulfur trioxide in DMSO and triethylamine. The aldehyde

10 **56a.4** is then converted to the epoxide **3.1** by treatment with chloromethylbromide and excess lithium in THF at −65 °C. A mixture of isomers are produced which are separated by chromatography.

Scheme **57** depicts the preparation of epoxides **57.4** incorporating a phosphonate group linked

15 to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **57.1** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **57.2**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be

20 employed. If X is CH_2OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **57.3**, which, employing the sequence of reactions shown in Scheme **56** or **56a**, is transformed into the epoxide **57.4**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester,

25 **57.5** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **57.6**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **57.5**. The latter compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **57.8**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **57.1**

30 in place of **57.5**, and/or different phosphonates **57.2**, the corresponding products **57.4** are obtained.

Scheme 58 illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative 58.1 is reacted with a dialkyl bromoalkyl phosphonate 58.2 to afford the product 58.3. The reaction is conducted in a polar

5   organic solvent such as dimethylformamide or acetonitrile, in the presence of a suitable base such as sodium hydride or cesium carbonate. The product is then transformed, using the sequence of reactions shown in Scheme 56, into the epoxide 58.4.

For example, the protected aminoacid 58.5, prepared as described above (Scheme 56) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with

10   a dialkyl 2-bromoethyl phosphonate 58.6, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product 58.7. The latter compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide 58.8.

Using the above procedures, but employing different phenols, thiols, and amines 58.1 in place

15   of 58.5, and/or different phosphonates 58.2, the corresponding products 58.4 are obtained.

Scheme 59 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.
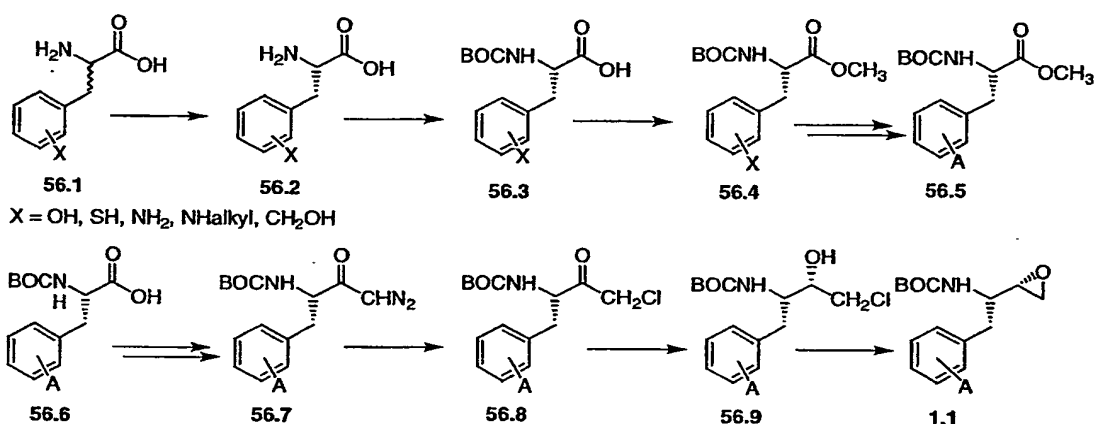
20   In this procedure, a protected hydroxymethyl-substituted phenylalanine 59.1 is converted into the halomethyl-substituted compound 59.2. For example, the carbinol 59.1 is treated with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 108, 1035, 1986 to afford the product 59.2 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 59.3. The reaction is accomplished in

25   the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 59.4, which, employing the sequence of reactions shown in

30   Scheme 56, is transformed into the epoxide 59.5.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 59.6, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in

Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **59.7**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **59.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **59.9**. The latter

5   compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **59.10**.

Using the above procedures, but employing different carbinols **59.1** in place of **59.6**, and/or different phosphonates **59.3**, the corresponding products **59.5** are obtained.

Scheme 56

X = OH, SH, NH₂, NHalkyl, CH₂OH

Scheme 57

Method

X = OH, SH, NH₂, NHalkyl, CH₂OH

Example

10
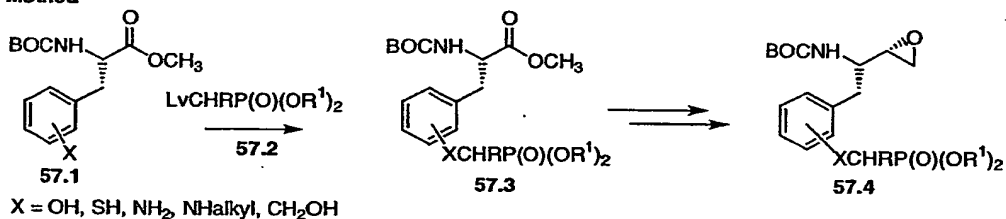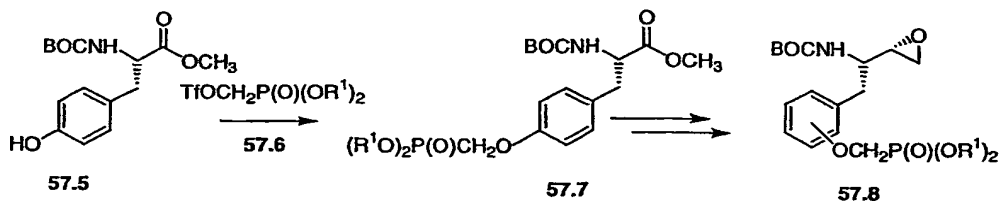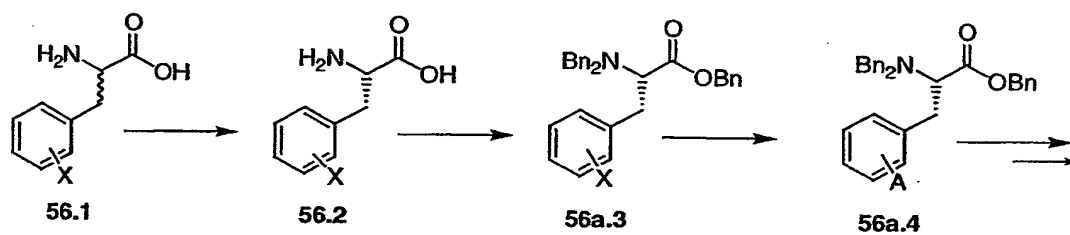
Scheme 56a

X = OH, SH, NH$_2$, NHalkyl, CH$_2$OH
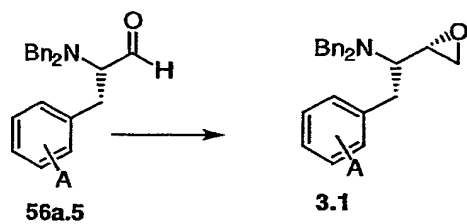
Scheme 58

Method

X = OH, SH, NH₂, NHalkyl

58.1

Y = O, S, NH, Nalkyl

58.3

58.4

Example

58.5

58.7

58.8

Scheme 59

Method

Z = Cl, Br

X = O, S, NH

59.3

59.1

59.2

59.4

59.5

Example

59.6

59.7

59.8

59.9

59.10
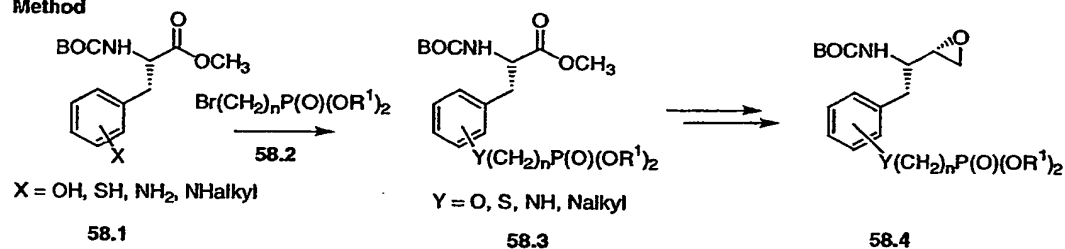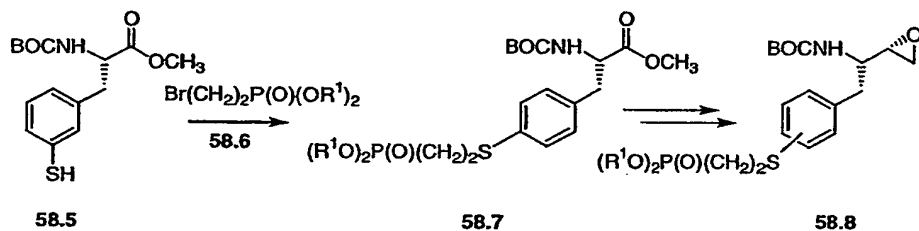
Preparation of phenylalanine derivatives 2.1 incorporating phosphonate moieties or precursors thereto.

5

Scheme **60** illustrates the preparation of the hydroxymethyl oxazolidine derivative **2.1**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this reaction sequence, the substituted phenylalanine **60.1**, in which A is as defined above, is transformed, via the intermediates **60.2** - **60.9**, into the hydroxymethyl

5   product **2.1**. In this procedure, phenylalanine, or a substituted derivative thereof, **60.1**, is converted into the phthalimido derivative **60.2**. The conversion of amines into phthalimido derivatives is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in

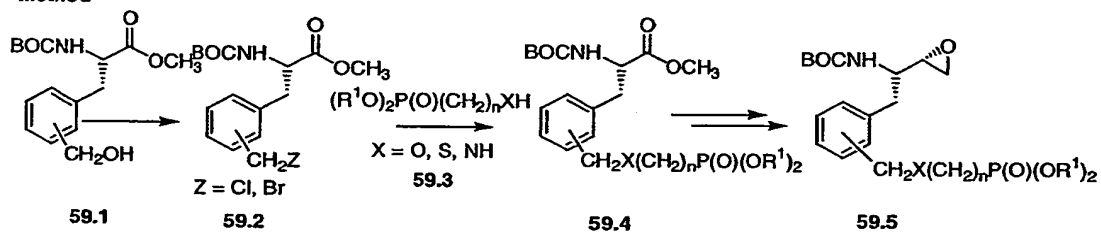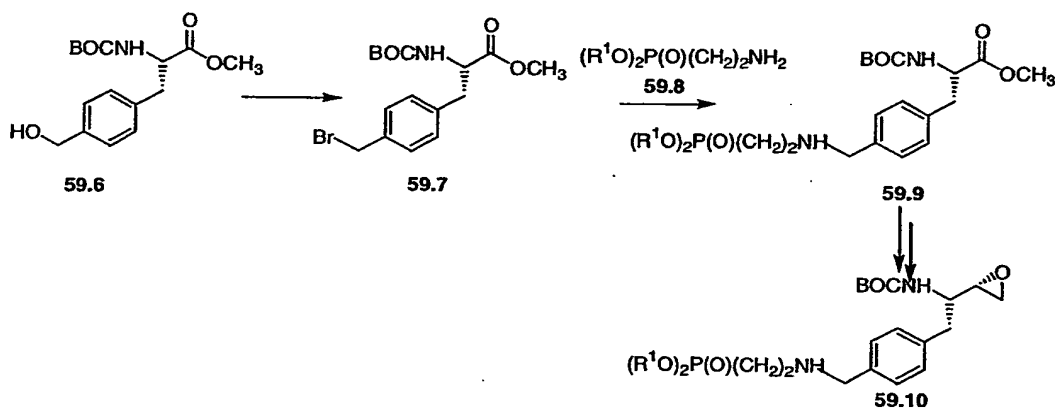10   the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine **60.2**. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride **60.3**, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a

15   reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride **60.3**,

20   X = Cl, is then converted into the aldehyde **60.4** by means of a reduction reaction. This procedure is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy

25   hydride or triethylsilane. Preferably, the acid chloride **60.3** X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of butylene oxide, as described in WO 9607642, to afford the aldehyde **60.4**. The aldehyde **60.4** is then transformed into the cyanohydrin derivative **60.5**. The conversion of aldehydes into cyanohydrins is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley,

30   Second Edition 1990, p. 211. For example, the aldehyde **60.4** is converted into the cyanohydrin **60.5** by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described

- 965 -

in WO 9607642, or by alternative methods described therein. The cyanohydrin is then
subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding
carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the
aminoacid **60.6** The hydrolysis reactions are effected by the use of aqueous mineral acid. For

5   example, the substrate **60.5** is reacted with aqueous hydrochloric acid at reflux, as described in
WO 9607642, to afford the carboxylic acid product **60.6**. The aminoacid is then converted
into a carbamate, for example the ethyl carbamate **60.7**. The conversion of amines into
carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and
P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate,

10   for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to
afford the carbamate **60.7**. For example, the aminoacid **60.6** is reacted, in aqueous solution,
with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as
described in WO 9607642, to afford the carbamate **60.7**. The latter compound is then
transformed into the oxazolidinone **60.8**, for example by treatment with aqueous sodium

15   hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid
is transformed into the methyl ester **60.9** by means of a conventional esterification reaction.
The conversion of carboxylic acids into esters is described for example, in Comprehensive
Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be
effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or

20   by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for
example an alkyl bromide. For example, the carboxylic acid **60.8** is converted into the methyl
ester **60.9** by treatment with methanol at reflux temperature, in the presence of a catalytic
amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the
compound **60.9** is then reduced to yield the corresponding carbinol **2.1**. The reduction of

25   carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by
R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing
agents such as borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride,
lithium aluminum hydride and the like. For example, the ester **60.9** is reduced to the carbinol
2.1 by reaction with sodium borohydride in ethanol at ambient temperature, as described in

30   WO 9607642.

The conversion of the substituent A into the group link-P(O)(OR^1)$_2$ may be effected at any
convenient step in the reaction sequence, or after the reactant **2.1** has been incorporated into

the intermediates **1**. Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **2.1** are shown below, (Schemes **61-62**)

Scheme **61** depicts the preparation of hydroxymethyloxazolidinones **61.9** in which the
5   phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **61.1** is converted, using the series of reactions illustrated in Scheme **60**, into the bromophenyloxazolidinone **61.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **61.3**, to afford the phosphonate product **61.4**. The reaction between aryl bromide and dialkyl phosphites to yield
10 aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **61.4** is then reduced with sodium borohydride to the corresponding
15 hydroxymethyl derivative **61.5**, using the procedure described above (Scheme **60**)
For example, 3-bromophenylalanine **61.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme **60**, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **61.7**. This compound is then coupled with a dialkyl phosphite **61.3**, in toluene solution at reflux, in the presence of a catalytic amount of
20 tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **61.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **61.9**.
Using the above procedures, but employing, in place of 3-bromophenylalanine **61.6** different bromophenylalanines **61.1** and/or different dialkyl phosphites **61.3**, the corresponding products
25 **61.5** are obtained.

Scheme **62** illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **62.9** and **62.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted
30 phenylalanine **62.1** is converted into the benzyl ester **62.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in

5   Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester 62.3 is then reacted

10   with phthalic anhydride, as described above (Scheme 60) to afford the phthalimide 62.4. The benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid 62.5. This compound is transformed, by means of the series of reactions shown in Scheme 60, into the carbomethoxy oxazolidinone 62.6, using in each step the same conditions as are described above (Scheme 60). The protected OH or

15   SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into

20   the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol 62.7 is then reacted with a hydroxyalkyl phosphonate 62.20 under the conditions of the Mitsonobu reaction, as described above (Scheme 49), to afford the ether or thioether 62.8. The latter compound is then reduced with sodium borohydride, as described

25   above (Scheme 60) to afford the hydroxymethyl analog 62.9.

Alternatively, the phenol or thiophenol 62.7 is reacted with a dialkyl bromoalkyl phosphonate 62.10 to afford the alkylation product 62.11. The alkylation reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium

30   carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound 62.12.

For example, 3-hydroxyphenylalanine **62.13** (Fluka) is converted in to the benzyl ester **62.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **62.15**. The protected ether is then reacted with phthalic anhydride, as described above

5   (Scheme 60) to yield the phthalimido-protected compound **62.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **62.17**. This compound is then transformed, by means of the series of reactions shown in Scheme 60, into the carbomethoxy-substituted oxazolidinone **62.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient

10 temperature, to produce the phenol **62.19**. The latter compound is reacted with a dialkyl hydroxymethyl phosphonate **62.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsonobu reaction. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and

15 R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction yields the phenolic ether **62.21**. The carbomethoxy group is then

20 reduced by reaction with sodium borohydride, as described above, to afford the carbinol **62.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **62.13**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl hydroxyalkyl phosphonates **62.20**, the corresponding products **62.9** are obtained.

25 As a further example of the methods illustrated in Scheme 62, 4-mercaptophenylalanine **62.23**, prepared as described in J. Am. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **62.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm.

30 Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **62.27**. The latter compound is then transformed, by means of the series of reactions

shown in Scheme 60, into the carbomethoxy oxazolidinone 62.28. The adamantyl protecting group is then removed by treatment of the thioether 62.28 with mercuric acetate in trifluoroacetic acid at 0°, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol 62.29. The thiol is then reacted with one molar equivalent of a dialkyl

5   bromoethylphosphonate 62.30, (Aldrich) and cesium carbonate in dimethylformamide at 70°, to afford the thioether product 62.31. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol 62.32.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine 62.23, different hydroxy or mercapto-substituted phenylalanines 62.1, and/or different dialkyl

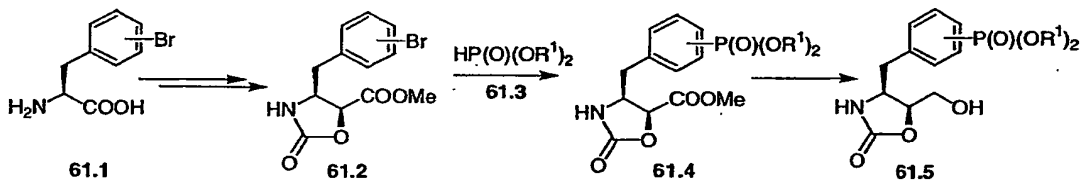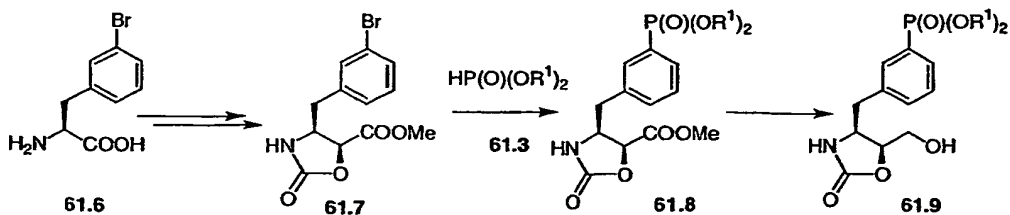10   bromoalkyl phosphonates 62.10, the corresponding products 62.12 are obtained.
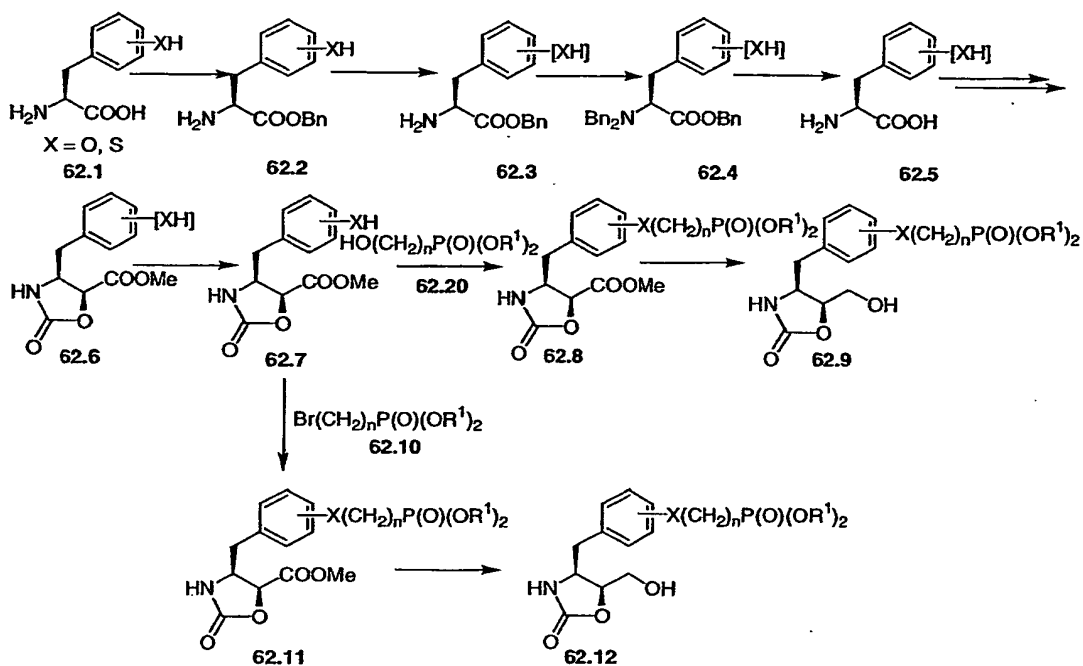
Scheme 60
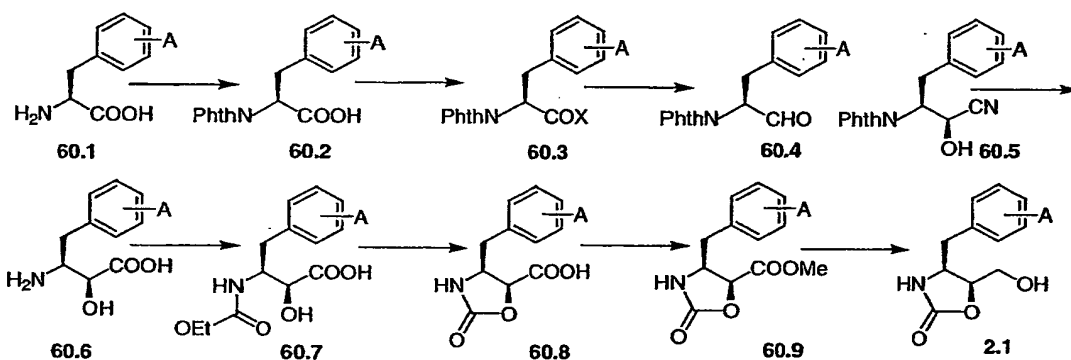
Scheme61

Method

Example

Scheme 62

Method

Scheme 62 Example 1

5
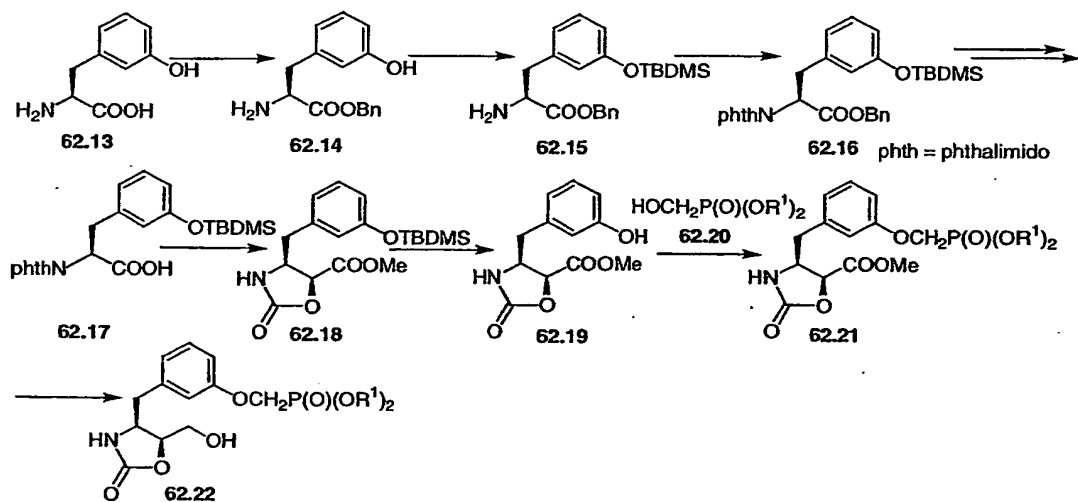
Scheme 62 Example 2

adm = adamantyl
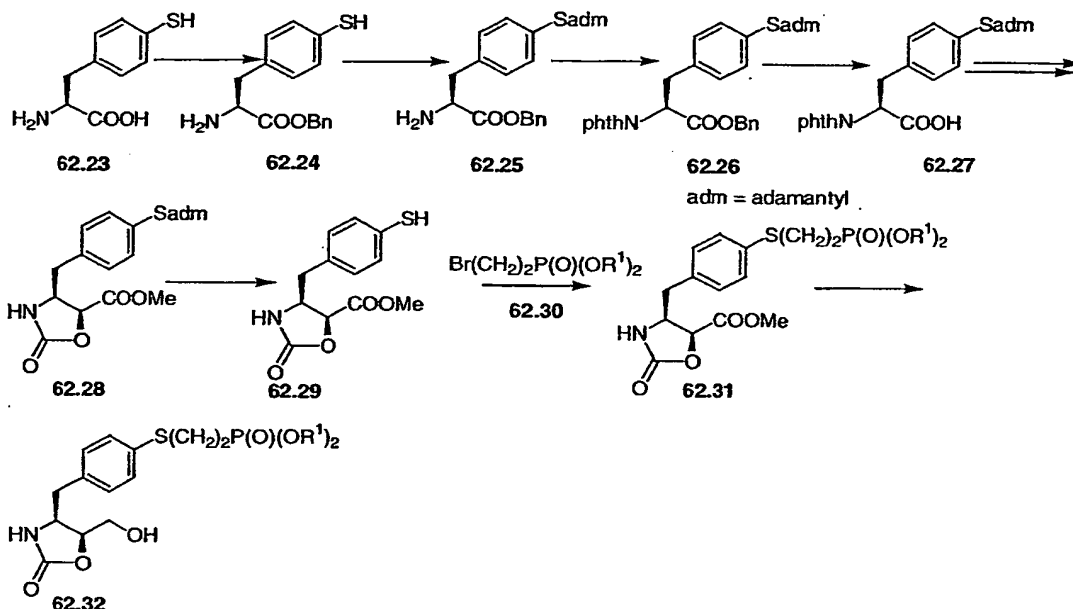
Preparation of the phosphonate-containing thiophenol derivatives 7.2.

5   Schemes **63** - **83** describe the preparation of phosphonate-containing thiophenol derivatives
7.2 which are employed as described above (Schemes **7** - **9**) in the preparation of the
phosphonate ester intermediates **1** in which X is sulfur.

Scheme **63** depicts the preparation of thiophenol derivatives in which the phosphonate moiety
10   is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol **63.1** is
protected to afford the product **63.2**. The protection of phenyl thiol groups is described in
Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second
Edition 1990, p. 277. For example, thiol substituents can be protected as trialkylsilyloxy
groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a
15   chlorotrialkylsilane and a base such as imidazole, for example as described in Protective
Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,
p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or
adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the
thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in

Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, with a dialkyl phosphite 63.3, to afford the phosphonate ester 63.4. The thiol protecting group is then removed, as described above, to afford the thiol 63.5.

5   For example, 3-bromothiophenol 63.6 is converted into the 9-fluorenylmethyl (Fm) derivative 63.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 63.3, as described above, to afford the phosphonate ester 63.8. The Fm protecting group is then removed by treatment of the product with piperidine in

10   dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 63.9.

Using the above procedures, but employing, in place of 3-bromothiophenol 63.6, different thiophenols 63.1, and/or different dialkyl phosphites 63.3, the corresponding products 63.5 are obtained.

15

Scheme 64 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 64.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 64.3. The latter compound is reacted

20   with a halodialkyl phosphite 64.4 to afford the product 64.5; deprotection then affords the thiophenol 64.6

For example, 4-bromothiophenol 64.7 is converted into the S-triphenylmethyl (trityl) derivative 64.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative 64.9

25   by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite 64.10 to afford the phosphonate 64.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 64.12.

Using the above procedures, but employing, in place of the bromo compound 64.7, different

30   halo compounds 64.1, and/or different halo dialkyl phosphites 64.4, there are obtained the corresponding thiols 64.6.

Scheme 65 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 65.1 is subjected to free-radical bromination to afford a bromomethyl product 65.2. This compound is reacted with a sodium dialkyl phosphite 65.3

5   or a trialkyl phosphite, to give the displacement or rearrangement product 65.4, which upon deprotection affords the thiophenol 65.5.

For example, 2-methylthiophenol 65.6 is protected by conversion to the benzoyl derivative 65.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate

10   to yield the bromomethyl product 65.8. This material is reacted with a sodium dialkyl phosphite 65.3, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 65.9. Alternatively, the bromomethyl compound 65.8 is converted into the phosphonate 65.9 by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound 65.8 is heated with a trialkyl

15   phosphate $P(OR^1)_3$ at ca. 100^0 to produce the phosphonate 65.9. Deprotection of the phosphonate 65.9, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol 65.10.

Using the above procedures, but employing, in place of the bromomethyl compound 65.8, different bromomethyl compounds 65.2, there are obtained the corresponding thiols 65.5.

20

Scheme 66 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol 66.1 is reacted with a dialkyl hydroxyalkylphosphonate 66.2 under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42,

25   335, to afford the coupled product 66.3. Deprotection then yields the O- or S-linked products 66.4.

For example, the substrate 3-hydroxythiophenol, 66.5, is converted into the monotrityl ether 66.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl

30   phosphonate 66.7 in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound 66.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 66.9.

- 974 -

Using the above procedures, but employing, in place of the phenol **66.5**, different phenols or thiophenols **66.1**, there are obtained the corresponding thiols **66.4**.

Scheme 63
Method

63.1
Ha = halogen

Example

Fm = 9-fluorenylmethyl
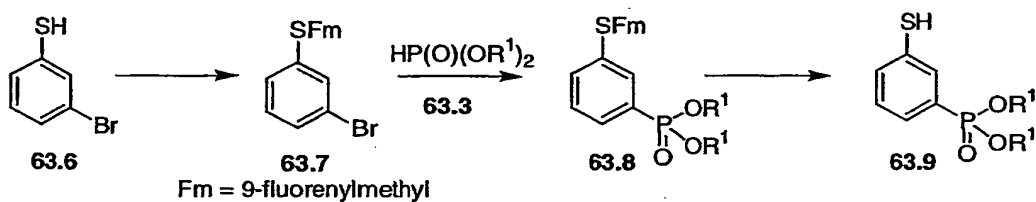
5

Scheme 64
Method

Example

Scheme 65

Method

Example

Scheme 66

Method

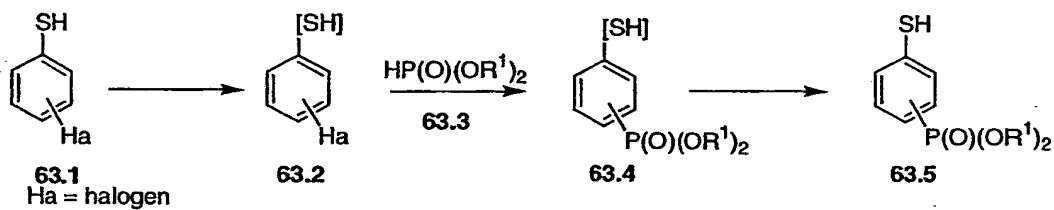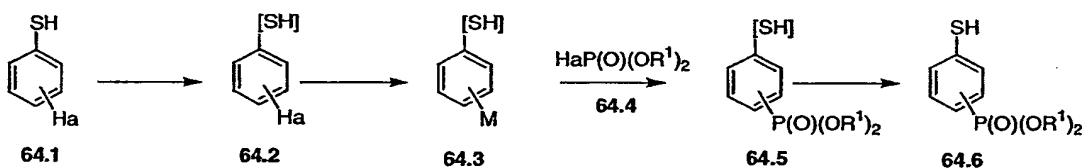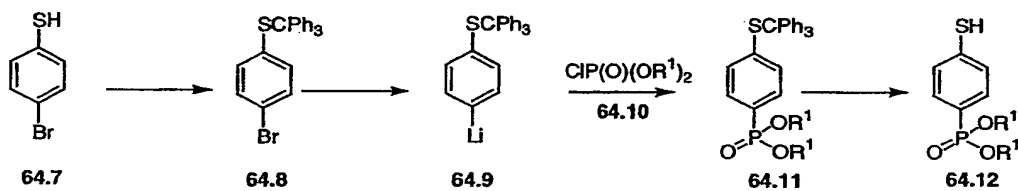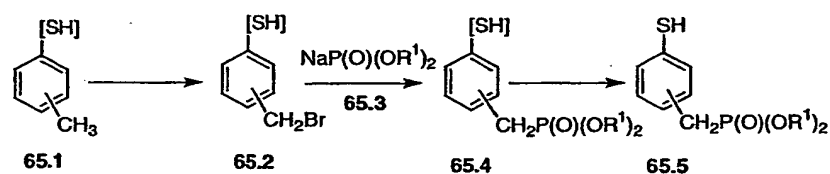X=O, S
66.1

Example

Tr=triphenylmethyl
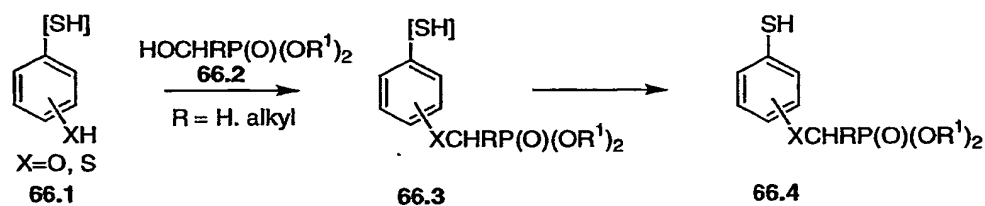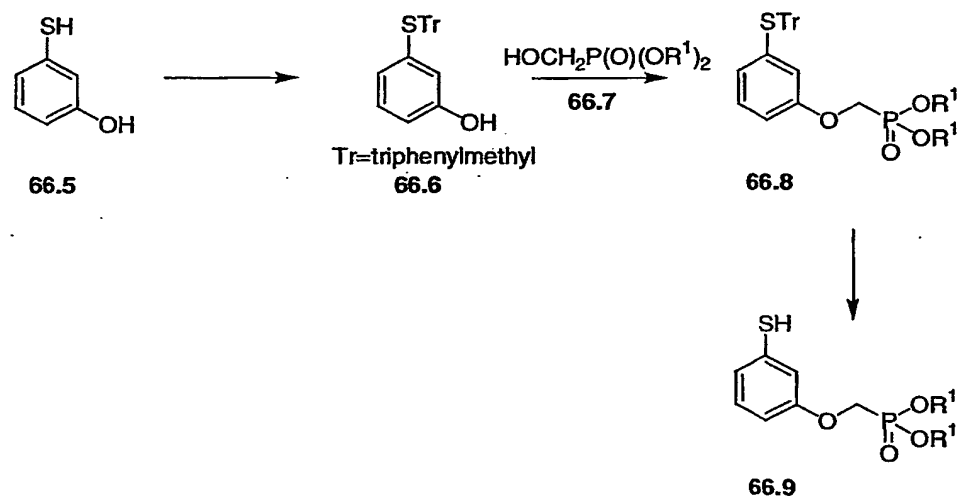**66.6**

5
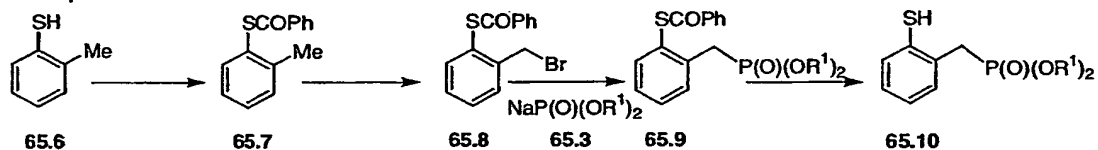
Scheme **67** illustrates the preparation of thiophenols **67.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **67.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **67.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled

5   product **67.3**. Deprotection then affords the thiol **67.4**.

For example, 4-methylaminothiophenol **67.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product **67.6**. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl

10   phosphonate **67.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **67.8**. Preferably, equimolar amounts of the phosphonate **67.7** and the amine **67.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **67.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide

15   for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **67.9**.

Using the above procedures, but employing, in place of the thioamine **67.5**, different phenols, thiophenols or amines **67.1**, and/or different phosphonates **67.2**, there are obtained the corresponding products **67.4**.

20

Scheme **68** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **68.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **68.1** is reacted with a dialkyl bromoalkyl

25   phosphonate **68.2** to afford the product **68.3**. Deprotection then affords the free thiophenol **68.4**.

For example, 3-hydroxythiophenol **68.5** is converted into the S-trityl compound **68.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **68.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction

30   is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

potassium iodide, at about 50°, to yield the ether product **68.8**. Deprotection, as described above, then affords the thiol **68.9**.

Using the above procedures, but employing, in place of the phenol **68.5**, different phenols, thiophenols or amines **68.1**, and/or different phosphonates **68.2**, there are obtained the
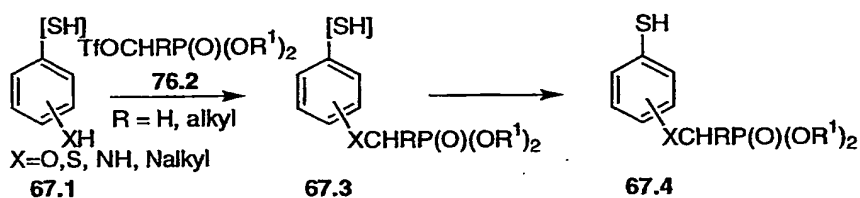
5   corresponding products **68.4**.

Scheme **69** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **69.2** is

10   coupled with an aromatic bromo compound **69.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as

15   tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **69.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **69.4**, or the saturated analog **69.6**.

20   For example, 3-bromothiophenol is converted into the S-Fm derivative **69.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **69.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar

25   solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **69.9**. Deprotection, as described above, then affords the thiol **69.10**. Optionally, the initially formed unsaturated phosphonate **69.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **69.11**, which upon deprotection affords the thiol **69.12**.

30   Using the above procedures, but employing, in place of the bromo compound **69.7**, different bromo compounds **69.1**, and/or different phosphonates **69.2**, there are obtained the corresponding products **69.4** and **69.6**

Scheme 67

Method

[SH]   TfOCHRP(O)(OR^1)$_2$ [SH]   SH

$\xrightarrow[\text{R = H, alkyl}]{\text{76.2}}$

X=O,S, NH, Nalkyl   XCHRP(O)(OR^1)$_2$ XCHRP(O)(OR^1)$_2$

67.1   **67.3**   **67.4**

Example

SH   SAc   TrOCH$_2$P(O)(OR^1)$_2$ SAc   SH

$\xrightarrow{\text{67.7}}$

Me^NH   Me^NH   Me–N $\overset{O}{\underset{OR^1}{\overset{||}{P}}}$OR^1 Me–N $\overset{O}{\underset{OR^1}{\overset{||}{P}}}$OR^1

67.5   **67.6**   **67.8**   **67.9**

Scheme 68

Method

[SH]   Br(CH$_2$)$_n$P(O)(OR^1)$_2$ [SH]   SH

$\xrightarrow{\text{68.2}}$

X=O,S,NH,Nalkyl   X(CH$_2$)$_n$P(O)(OR^1)$_2$ X(CH$_2$)$_n$P(O)(OR^1)$_2$

68.1   **68.3**   **68.4**

Example

SH   STr   Br(CH$_2$)$_4$P(O)(OR^1)$_2$ STr

$\xrightarrow{\text{68.7}}$

OH   OH   O(CH$_2$)$_4$P(O)(OR^1)$_2$

Tr=triphenylmethyl

68.5   **68.6**   **68.8**

SH

O(CH$_2$)$_4$P(O)(OR^1)$_2$

68.9
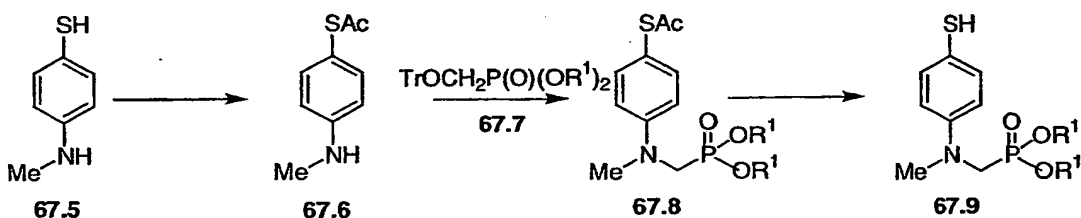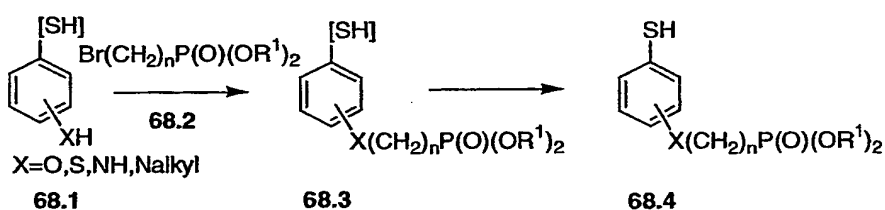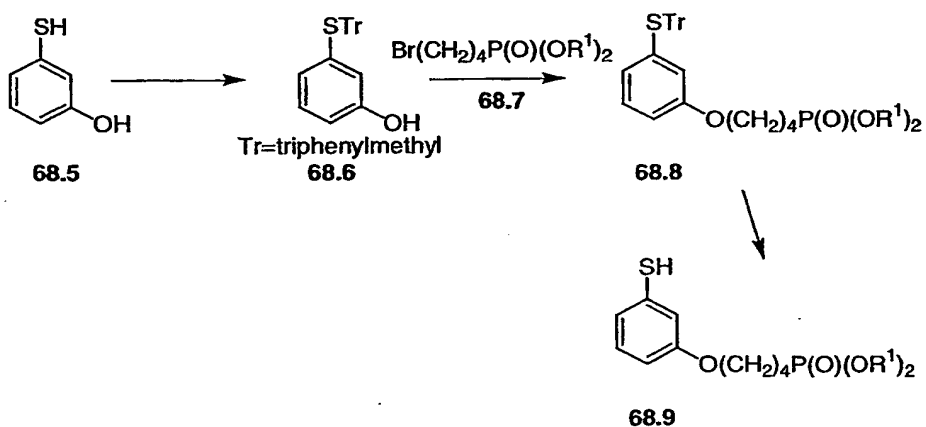
Scheme 69

Method
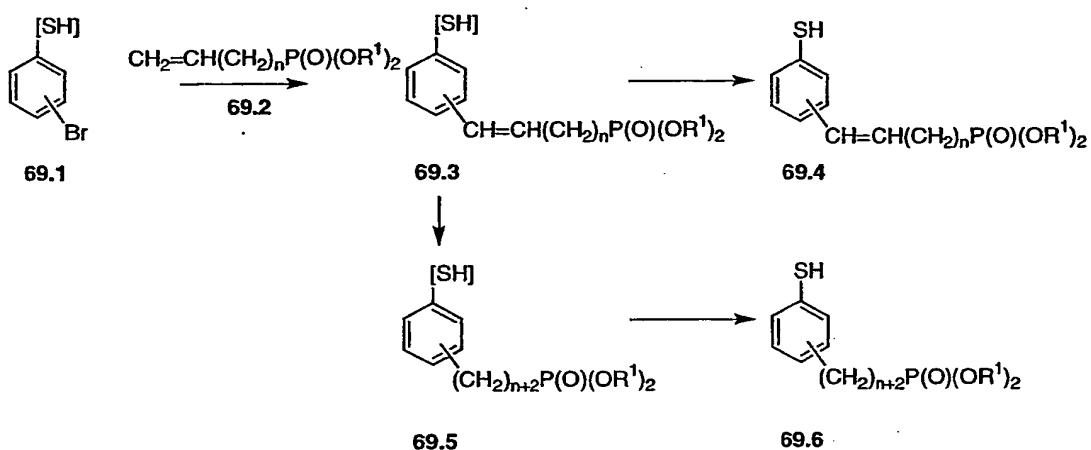
Example
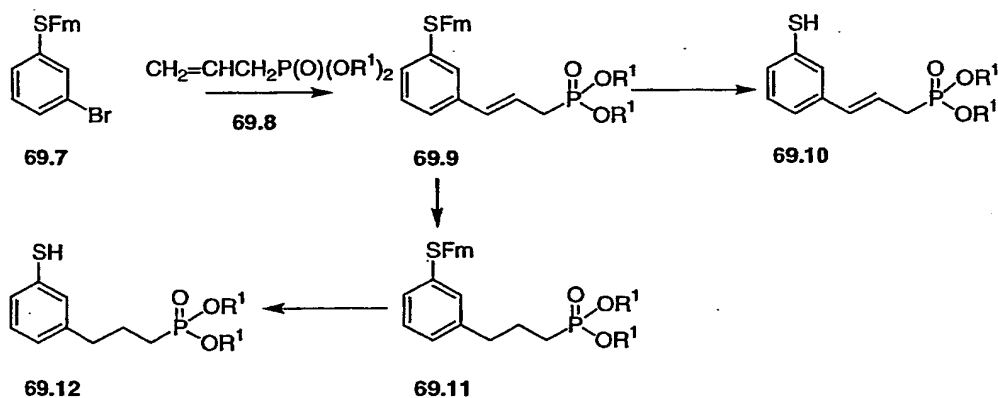
Scheme **70** illustrates the preparation of an aryl-linked phosphonate ester **70.4** by means of a

5   palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a

phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock,

VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **70.1** is obtained by means of a

metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for

example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the

10   diaryl product **70.3** which is deprotected to yield the thiol **70.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane,

in the presence of a base such as imidazole, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation

with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords

the boronate **70.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **70.6**, the

preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the

5   presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium

carbonate, to afford the coupled product **70.7**. Deprotection, for example by the use of

tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **70.8**.

Using the above procedures, but employing, in place of the boronate **70.5**, different boronates

70.1, and/or different phosphonates **70.2**, there are obtained the corresponding products **70.4**.

10   Scheme **71** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is

linked to the thiophenyl group by means of a chain which incorporates an aromatic or

heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol

71.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **71.2**,

prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a

15   bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction

product **71.3** is then deprotected to afford the thiol **71.4**. For example, 1,4-dimercaptobenzene

is converted into the monobenzoyl ester **71.5** by reaction with one molar equivalent of benzoyl

chloride, in the presence of a base such as pyridine. The monoprotected thiol **71.5** is then

reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **71.6**, the preparation of which is

20   described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as

dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The

thioether product **71.7** thus obtained is deprotected, as described above, to afford the thiol

71.8.

Using the above procedures, but employing, in place of the thiophenol **71.5**, different phenols,

25   thiophenols or amines **71.1**, and/or different phosphonates **71.2**, there are obtained the

corresponding products **71.4**.

Scheme **72** illustrates the preparation of phosphonate-containing thiophenols in which the

attached phosphonate chain forms a ring with the thiophenol moiety.

30   In this procedure, a suitably protected thiophenol **72.1**, for example an indoline (in which X-Y

is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted

with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **72.2**, in the presence of an

organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **72.3**. Deprotection, as described above, then affords the thiol **72.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding

5   hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

10   J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

15   For example, 2,3-dihydro-1H-indole-5-thiol, **72.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **72.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **72.7**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, to yield the phosphonate **72.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as

20   described above, then affords the thiol **72.9**.

Using the above procedures, but employing, in place of the thiol **72.5**, different thiols **72.1**, and/or different triflates **72.2**, there are obtained the corresponding products **72.4**.

Scheme 70

Method
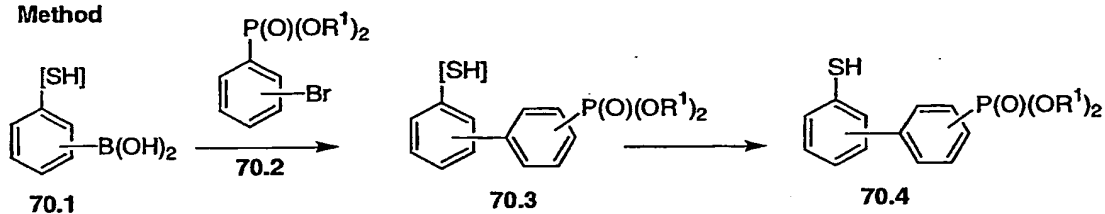
Example

Scheme 71

Method

X =O, S, NH, Nalkyl

Example

5   **Preparation of phosphonate-containing analogs of isobutylamine 10.2.**

Schemes 73 - 75 illustrate the preparation of the phosphonate-containing analogs of isobutylamine which are employed in the preparation of the phosphonate esters 2.

Scheme 73 depicts the preparation of phosphonates which are attached to the isobutylamine
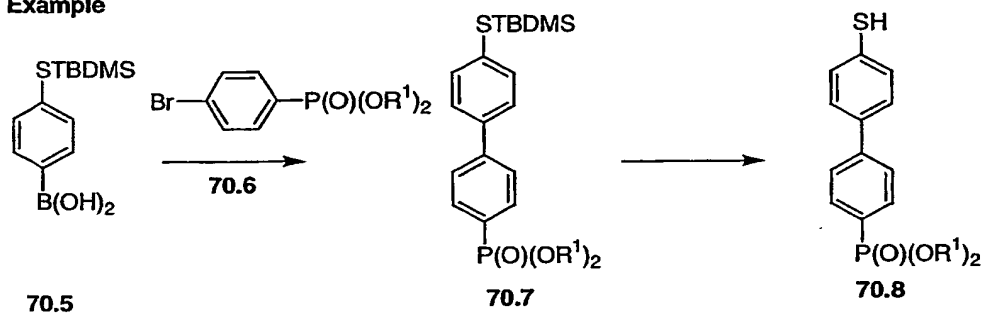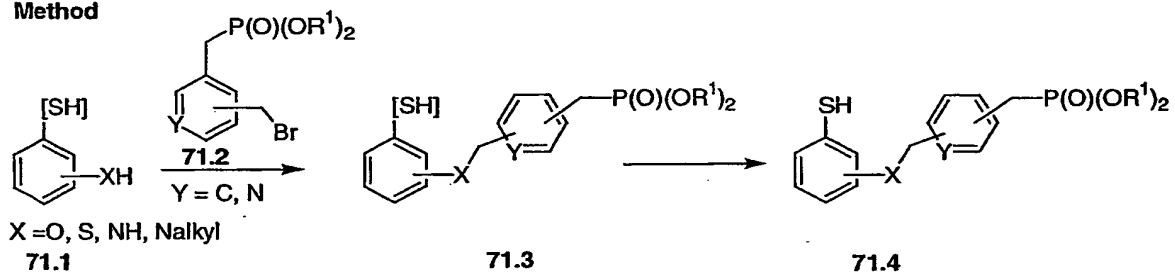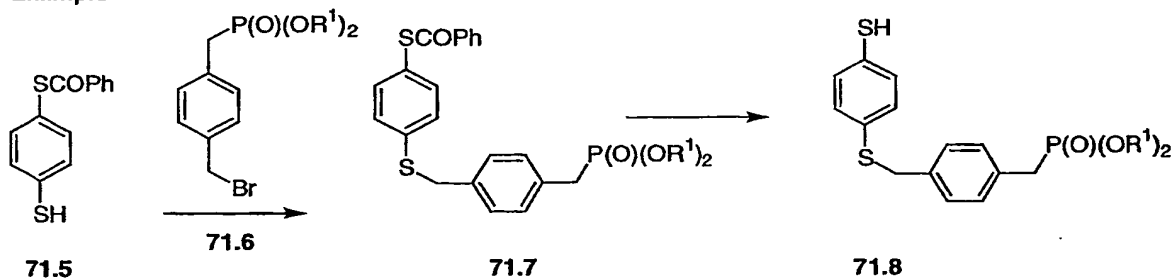5   by means of an amide linkage. In this procedure, an aminoacid 73.1 is protected to afford the product 73.2. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, 309. Amino groups are protected, for example, by conversion into carbamates such as the tert. butoxycarbamate (BOC) derivative, or by reaction with phthalic anhydride to afford the phthalimido (phth)
10   derivative. The amine-protected aminoacid 73.2 is then coupled with a dialkyl aminoalkyl phosphonate 73.3, to yield the amide 73.4. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with
15   the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as
20   the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The protecting group is then removed to afford the amine 73.5. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 309ff. For example, BOC groups are removed by treatment
25   with acids such as trifluoroacetic acid, and phthalimido groups are removed by reaction with hydrazine hydrate.

For example, 2-methyl-4-aminobutyric acid 73.6 (Acros) is reacted with phthalic anhydride in refluxing toluene, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to give the phthalimido derivative 73.7. The
30   product is coupled with a dialkyl aminoethyl phosphonate 73.8, the preparation of which is described in J. Org. Chem., 2000, 65, 676,

- 984 -

in the presence of dicyclohexyl carbodiimide, to give the amide **73.9**. The protecting group is removed by reaction of the product with ethanolic hydrazine at ambient temperature, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to afford the amine **73.10**.

5   Using the above procedures, but employing, in place of the acid **73.6**, different acids **73.1**, and/or different amines **73.3**, the corresponding amides **73.5** are obtained.

Scheme **74** depicts the preparation of isobutylamine phosphonates in which the phosphonate is attached by means of an aromatic ring. In this procedure, 2-methyl-but-3-enylamine **74.1**,

10   prepared as described in Org. Prep. Proc. Int. 1976, 8, 75, is coupled, in the presence of a palladium catalyst, as described above (Scheme **50**) with a dialkyl bromophenyl phosphonate **74.2** to afford the olefinic product **74.3**. Optionally, the product is reduced to afford the saturated analog **74.4**. The reduction is effected catalytically, for example by the use of a palladium catalyst, or chemically, for example by the use of diimide.

15   For example, the amine **74.1** is coupled with a dialkyl 4-bromophenyl phosphonate **74.5**, prepared as described in J. Organomet. Chem., 1999, 581, 62, to yield the product **74.6**. Catalytic hydrogenation in ethanol, using a 5% palladium catalyst, then affords the saturated compound **74.7**.

Using the above procedures, but employing, in place of the phosphonate **74.5**, different

20   phosphonates **74.2** the corresponding products **74.3** and **74.4** are obtained.

Scheme **75** illustrates the preparation of isobutylamine phosphonates in which the phosphonate group is attached by means of an alkylene chain. In this procedure, a bromoamine **75.1** is protected, as described in Scheme **73**, to afford the derivative **75.2**. The product is then

25   reacted with a trialkyl phosphite **75.3**, in an Arbuzov reaction, as described in Scheme **65**, to give the phosphonate **75.4**. Deprotection then affords the amine **75.5**.

For example, 4-bromo-2-methyl-butylamine **75.6**, prepared as described in Tet., 1998, 54, 2365, is converted, as described above, into the phthalimido derivative **75.7**. The product is then heated at 110° with a trialkyl phosphite **75.3** to yield the phosphonate **75.8**, which upon

30   reaction with ethanolic hydrazine affords the amine **75.9**.

Using the above procedures, but employing, in place of the bromide **75.6**, different bromides **75.1**, and/or different phosphites **75.3**, the corresponding products **75.5** are obtained.

Scheme 72

Method

72.1

X-Y = $(CH_2)_{2,3}$; CH=CH
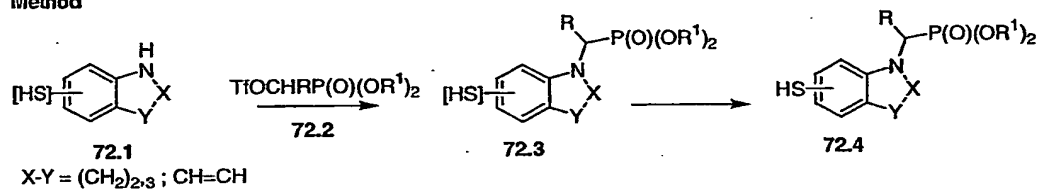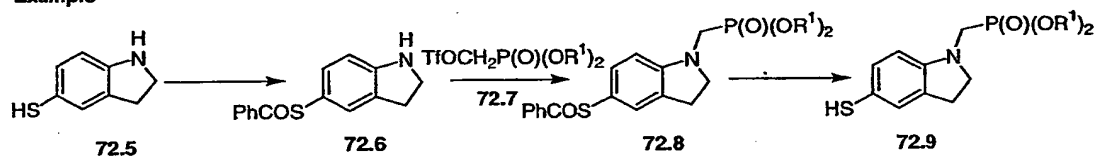
Example

Scheme 73

Method

Example

5
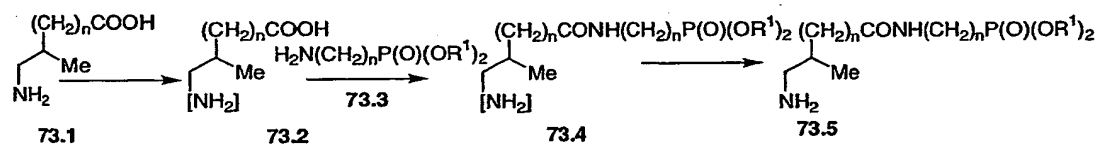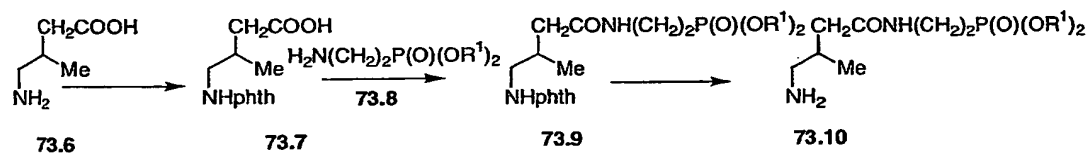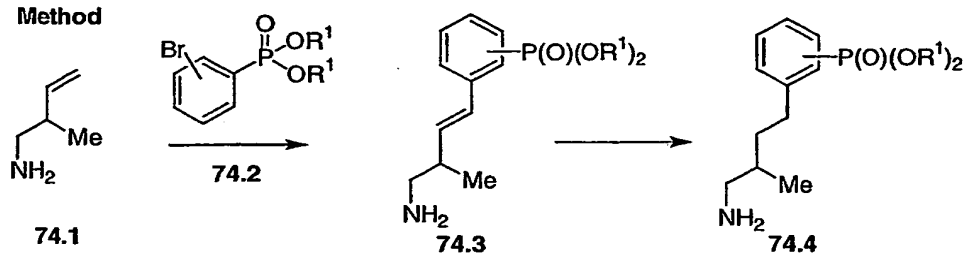
Scheme 74

Method

Example
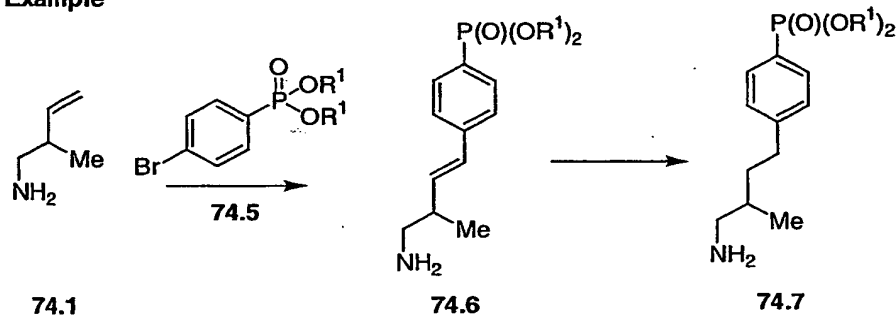
Scheme 75

Method
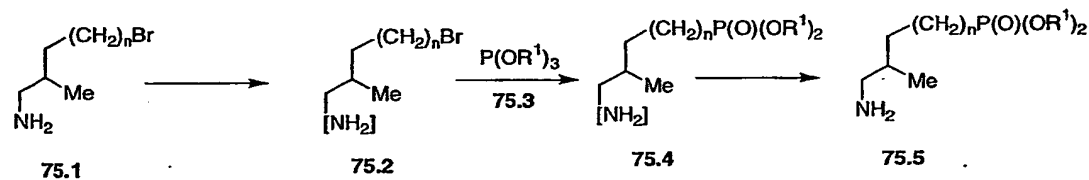
Example
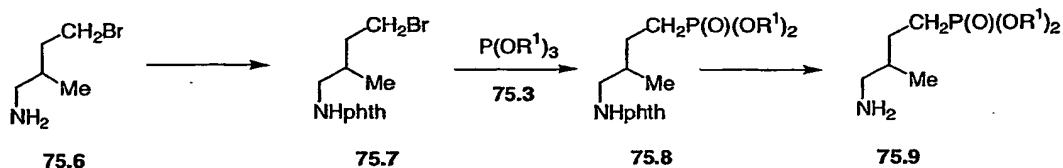
Preparation of cyclopentylmethylamine phosphonates.

Schemes **76 - 78** illustrate the preparation of cyclopentylmethylamine phosphonates which are employed, as shown in Schemes **10 - 12**, in the preparation of the phosphonate esters **3**.

Scheme **76** depicts the preparation of phosphonates attached to the cyclopentyl ring either directly or by means of an alkoxy link. In this procedure, a hydroxy-substituted

cyclopentylmethylamine **76.1** is protected, and the protected derivative **76.2** is converted into
the corresponding bromide **76.3**, for example by treatment with carbon tetrabromide and
triphenyl phosphine as described in Scheme **59**. The bromo compound is then reacted with a
trialkyl phosphite **76.4** in an Arbuzov reaction, as described above, to afford the phosphonate

5   **76.5** which is then deprotected to give the amine **76.6**. Alternatively, the protected amine **76.2**
is reacted with a dialkyl bromoalkyl phosphonate **76.7** to give the ether **76.8**. The alkylation
reaction is conducted at ca 100° in a polar organic solvent such as dimethylformamide in the
presence of a base such as sodium hydride or lithium hexamethyl disilylazide. The product is
then deprotected to give the amine **76.9**.

10   For example, 3-aminomethyl-cyclopentanol **76.10**, prepared as described in Tet., 1999, 55,
10815, is converted, as described above, into the phthalimido derivative **76.11**. The product is
then converted, as described above, into the bromo analog **76.12**. The latter compound is
reacted at ca 120° with a trialkyl phosphite **76.4** to afford the phosphonate **76.13**, which upon
deprotection by reaction with hydrazine yields the amine **76.14**.

15   Using the above procedures, but employing, in place of the bromide **76.12**, different bromides
76.3, and/or different phosphites **76.4**, the corresponding products **76.6** are obtained.
Alternatively, 2-aminomethyl-cyclopentanol **76.15**, prepared as described in Tet., 1999, 55,
10815, is converted into the phthalimido derivative **76.16**. The product is then reacted in
dimethylformamide solution with an equimolar amount of a dialkyl bromopropyl phosphonate

20   **76.17**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and sodium hydride, to
give the ether **76.18**. Deprotection, as described above, then affords the amine **76.19**.
Using the above procedures, but employing, in place of the carbinol **76.15**, different carbinols
76.1, and/or different phosphonates **76.7**, the corresponding products **76.9** are obtained.

25   Scheme **77** illustrates the preparation of cyclopentylmethylamines in which the phosphonate
group is attached by means of an amide group. In this procedure, a carboxyalkyl-substituted
cyclopentylmethylamine **77.1** is protected to afford the derivative **77.2**. The product is then
coupled, as described above, (Scheme **1**) with a dialkyl aminoalkyl phosphonate **77.3** to yield
the amide **77.4**. Deprotection then affords the amine **77.5**.

30   For example, 3-aminomethyl-cyclopentanecarboxylic acid **77.6** prepared as described in J.
Chem. Soc. Perkin 2, 1995, 1381, is converted into the BOC derivative **77.7**, by reaction with
BOC anhydride in aqueous sodium hydroxide, as described in Proc. Nat. Acad. Sci., 69, 730,

- 988 -

1972. The product is then coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate **77.8** to produce the amide **77.9**. Removal of the BOC group, for example by treatment with hydrogen chloride in ethyl acetate, then affords the amine **77.10**. Using the above procedures, but employing, in place of the carboxylic acid **77.6**, different

5 carboxylic acids **77.1**, and/or different phosphonates **77.3**, the corresponding products **77.5** are obtained.

Scheme 78 illustrates the preparation of cyclopentylmethylamines in which the phosphonate group is attached by means of an aminoalkyl group. In this procedure, the more reactive amino

10 group of an amino-substituted cyclopentylmethylamine **78.1** is protected, to give the derivative **78.2**. The product is then coupled, by means of a reductive amination reaction, as described in Scheme 55, with a dialkyl formylalkyl phosphonate **78.3** to give the amine product **78.4**, which upon deprotection affords the amine **78.5**.

For example, 2-aminomethyl-cyclopentylamine **78.6** prepared as described in WO 9811052, is

15 reacted with one molar equivalent of phthalic anhydride in refluxing tetrahydrofuran, to yield the phthalimido derivative **78.7**. The latter compound is reacted, in the presence of sodium cyanoborohydride, with a dialkyl formylmethyl phosphonate **78.8**, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, to afford the product **78.9**. Deprotection, as described above, then yields the amine **78.10**.

20 Using the above procedures, but employing, in place of the diamine **78.6**, different diamines **78.1**, and/or different phosphonates **78.3**, the corresponding products **78.5** are obtained.

Scheme 76

Method
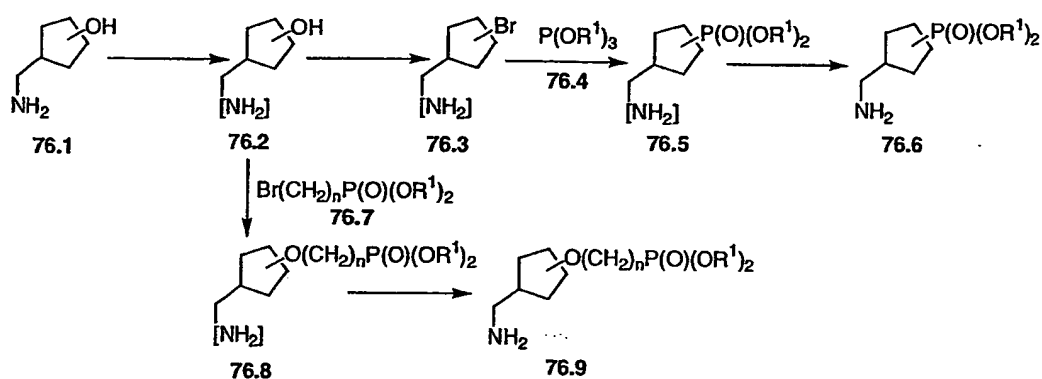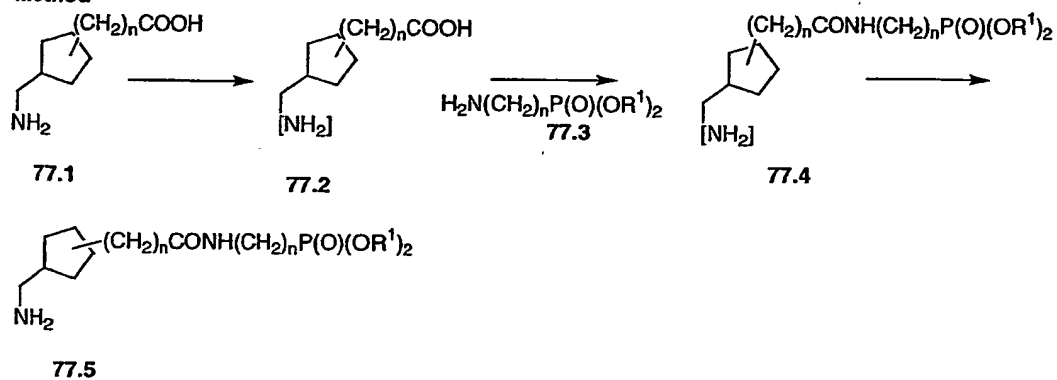
76.1 → 76.2 → 76.3 → P(OR¹)₃ 76.4 → 76.5 → 76.6

Br(CH₂)ₙP(O)(OR¹)₂
76.7

76.8 → 76.9

Example 1

76.10 → 76.11 → 76.12 → P(OR¹)₃ 76.4 → 76.13 → 76.14

Example 2

76.15 → 76.16 → Br(CH₂)₃P(O)(OR¹)₂ 76.17 → 76.18 → 76.19

Scheme 77

Method

77.1 → 77.2 → H₂N(CH₂)ₙP(O)(OR¹)₂ 77.3 → 77.4 →

77.5

Example

77.6 → 77.7 → H₂N(CH₂)₃P(O)(OR¹)₂ 77.8 → 77.9 → 77.10

Scheme 78

Method

78.1   78.2   (R^{1}O)$_2$P(O)(CH$_2$)$_n$CHO   78.4   78.5
                        78.3

Example

78.6   78.7   (R^{1}O)$_2$P(O)CH$_2$CHO   78.9   78.10
                        78.8
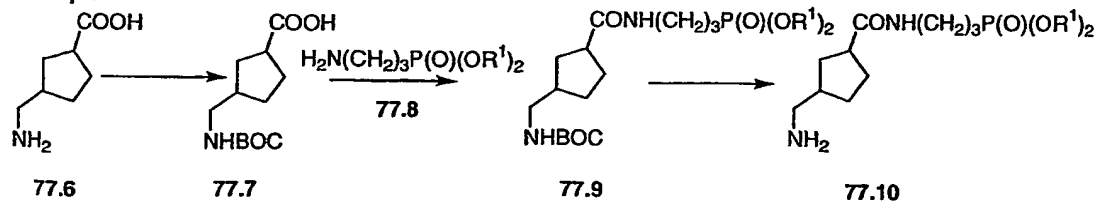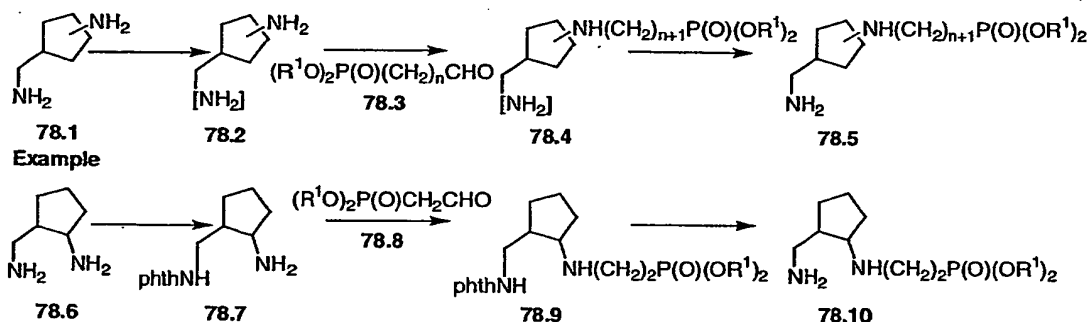
Preparation of phosphonate-substituted fluorobenzylamines 39.2.

Schemes **79** and **80** illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines **39.2** which are used in the preparation of the phosphonate esters **6**.

Scheme **79** depicts the preparation of fluorobenzylamines in which the phosphonate is attached by means of an amide or aminoalkyl linkage. In this procedure, the more reactive amino group in an amino-substituted 3-fluorobenzylamine **79.1** is protected. The product **79.2** is then coupled with a dialkyl carboxyalkyl phosphonate **79.3** to give the amide **79.4**, which upon deprotection yields the free amine **79.5**. Alternatively, the mono-protected diamine **79.2** is coupled, under reductive amination conditions, with a dialkyl formylalkyl phosphonate **79.6**, to produce the amine **79.7**, which upon deprotection affords the benzylamine **79.8**.

For example, 4-amino-3-fluorobenzylamine **79.9**, prepared as described in WO 9417035, is reacted in pyridine solution with one molar equivalent of acetic anhydride, to give the acetylamino product **79.10**. The product is reacted with a dialkyl carboxyethyl phosphonate **79.11**, (Epsilon) and dicyclohexyl carbodiimide, to afford the amide **79.12**. Deprotection, for example by reaction with 85% hydrazine, as described in J. Org. Chem., 43, 4593, 1978, then gives the amine **79.13**.
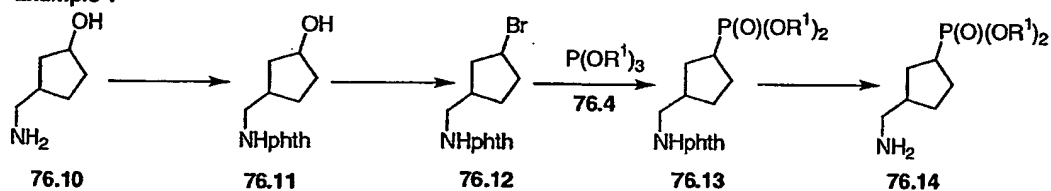
Using the above procedures, but employing, in place of the diamine **79.9**, different diamines **79.1**, and/or different phosphonates **79.3**, the corresponding products **79.5** are obtained.
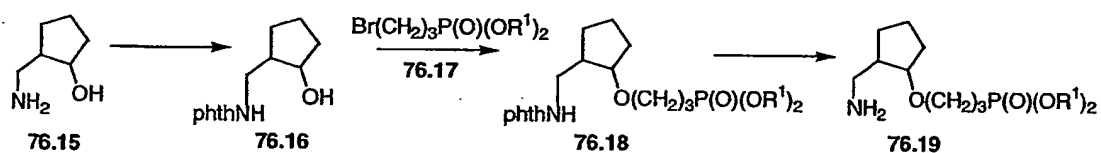
As a further example, the mono-protected diamine **79.10** is reacted, as described above, with a dialkyl formyl phosphonate **79.13**, (Aurora) and sodium cyanoborohydride, to give the amination product **79.14**. Deprotection then affords the amine **79.15**.

Using the above procedures, but employing, in place of the diamine **79.10** different diamines **79.2**, and/or different phosphonates **79.6**, the corresponding products **79.8** are obtained.

Scheme **80** depicts the preparation of fluorobenzylamines in which the phosphonate is attached
5   either directly or by means of a saturated or unsaturated alkylene linkage. In this procedure, a bromo-substituted 3-fluorobenzylamine **80.1** is protected. The product **80.2** is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme **50**, with a dialkyl alkenyl phosphonate **80.3**, to give the olefinic product **80.4** which upon deprotection affords the amine **80.5**. Optionally, the double bond is reduced, for example by catalytic
10   hydrogenation over a palladium catalyst, to yield the saturated analog **80.9**. Alternatively, the protected bromobenzylamine **80.6** is coupled, as described in Scheme **61**, in the presence of a palladium catalyst, with a dialkyl phosphite **80.6** to produce the phosphonate **80.7**. Deprotection then affords the amine **80.8**.

For example, 2-bromo-5-fluorobenzylamine **80.10**, (Esprix Fine Chemicals) is converted, as
15   described above, into the N-acetyl derivative **80.11**. The product is the coupled in dimethylformamide solution with a dialkyl vinyl phosphonate **80.12**, (Fluka) in the presence of palladium (II) acetate and triethylamine, to give the coupled product **80.13**. Deprotection then affords the amine **80.14** and hydrogenation of the latter compound yields the saturated analog **80.15**.

20   Using the above procedures, but employing, in place of the bromo compound **80.10** different bromo compounds **80.1**, and/or different phosphonates **80.3**, the corresponding products **80.5** and **80.9** are obtained.

As a further example, the protected amine **80.11** is coupled, in toluene at 100°, with a dialkyl phosphite **80.6**, in the presence of tetrakis(triphenylphosphine)palladium and a tertiary organic
25   base such as triethylamine, to give the phosphonate **80.16**. Deprotection then affords the amine **80.17**.

Using the above procedures, but employing, in place of the bromo compound **80.11** different bromo compounds **80.2**, and/or different phosphites **80.6**, the corresponding products **80.8** are obtained.
30

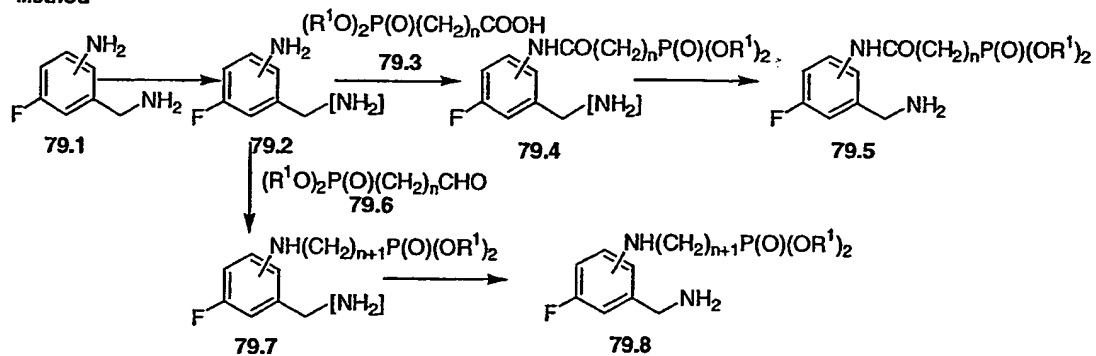**Scheme 79**

Method

Example 1
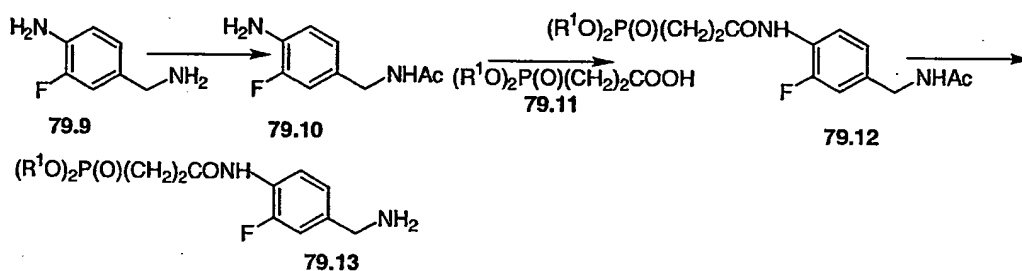
Example 2
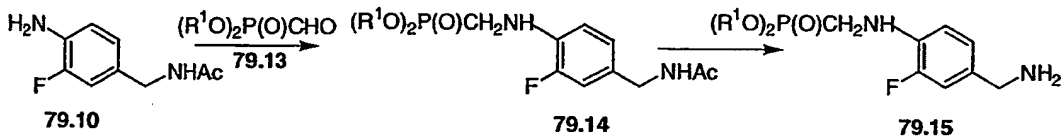
Scheme 80

Method

$CH_2=CH(CH_2)_nP(O)(OR^1)_2$
80.3

80.1 → **80.2** → **80.4** → **80.5**

$HP(O)(OR^1)_2$
80.6

80.7 → **80.8**

80.9

Example 1

$CH_2=CHP(O)(OR^1)_2$
80.12

80.10 → **80.11** → **80.13**

80.14 → **80.15**

Example 2

$HP(O)(OR^1)_2$
80.6

80.11 → **80.16** → **80.17**
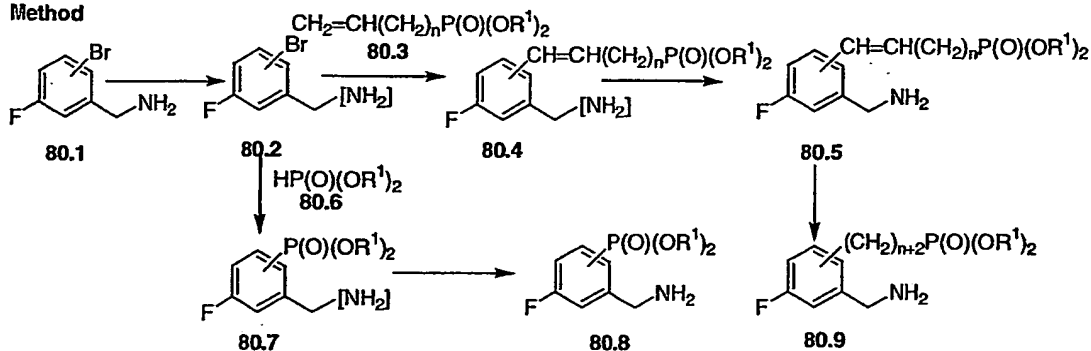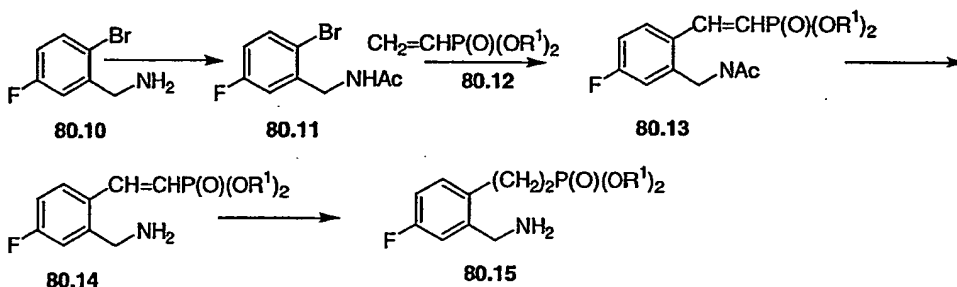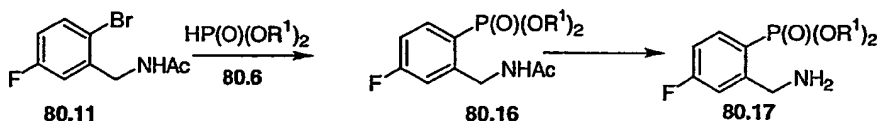
Preparation of phosphonate-substituted fluorobenzylamines 39.4.

5   Schemes **81** and **82** illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines **39.4** which are used in the preparation of the phosphonate esters **7**.

Scheme **81** depicts the preparation of 3-fluorobenzylamines in which the phosphonate group is attached by means of an amide linkage. In this procedure, 3-fluorophenylalanine **81.1**, (Alfa

10   . Aesar) is converted into the BOC derivative **81.2**. The product is then coupled with a dialkyl aminoalkyl phosphonate **81.3** to afford the amide **81.4**, which upon deprotection gives the amine **81.5**.

For example, the BOC-protected aminoacid **81.2** is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminomethyl phosphonate **81.6** (Interchim), to prepare the amide

15   **81.7**. Deprotection then affords the amine **81.8**.

Using the above procedures, but employing, in place of the amine **81.6** different amines **81.3**, the corresponding products **81.5** are obtained.

5   Scheme 82 illustrates the preparation of fluorobenzylamine derivatives in which the phosphonate group is attached by means of an alkyl or alkoxy chain. In this procedure, a hydroxyalkyl-substituted 3-fluorobenzylamine **82.1** is converted into the BOC derivative **82.2**. This compound is then reacted with a dialkyl bromoalkyl phosphonate **82.3** to give the ether **82.4**. The alkylation reaction is conducted in a polar organic solvent such as N-methylpyrrolidinone in the presence of a strong base such as sodium bis(trimethylsilyl)amide.

10   Deprotection of the product then affords the amine **82.5**. Alternatively, the N-protected carbinol **82.2** is converted into the corresponding bromide **82.6**, for example by reaction with N-bromoacetamide and triphenyl phosphine. The bromo compound is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described above, to give the phosphonate **82.8**, which upon deprotection affords the amine **82.9**.

15   For example, 2-amino-2-(3-fluoro-phenyl)-ethanol **82.10**, prepared as described in DE 4443892, is converted into the BOC derivative **82.11**. The latter compound is then reacted in dimethylformamide at 100° with a dialkyl bromoethyl phosphonate **82.12** (Aldrich) and sodium hydride, to give the ether product **82.13**. Removal of the BOC group then yields the amine **82.14**.

20   Using the above procedures, but employing, in place of the carbinol **82.10** different carbinols **82.1**, and/or different phosphonates **82.3** the corresponding products **82.5** are obtained.
As a further example, the BOC-protected carbinol **82.11** is reacted with carbon tetrabromide and triphenylphosphine to produce the bromo compound **82.15**. This material is heated at 120° with an excess of a trialkyl phosphite **82.7** to give the phosphonate **82.16**. Deprotection then

25   yields the amine **82.17**.
Using the above procedures, but employing, in place of the carbinol **82.11** different carbinols **82.2**, and/or different phosphonates **82.7** the corresponding products **82.9** are obtained.

Scheme 81

Method

Example

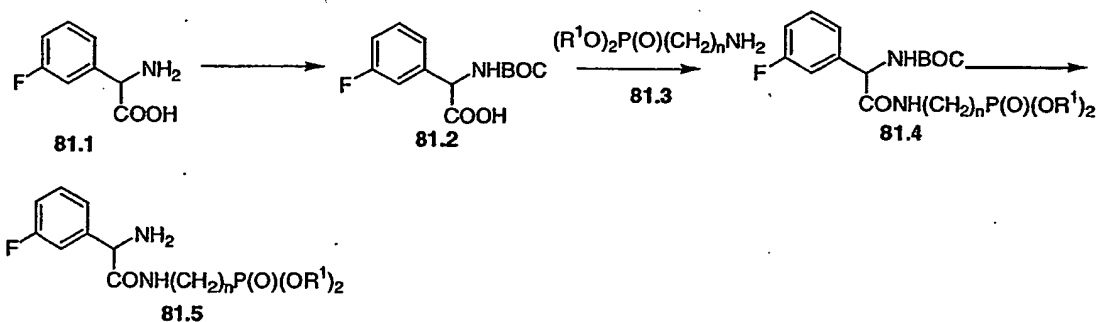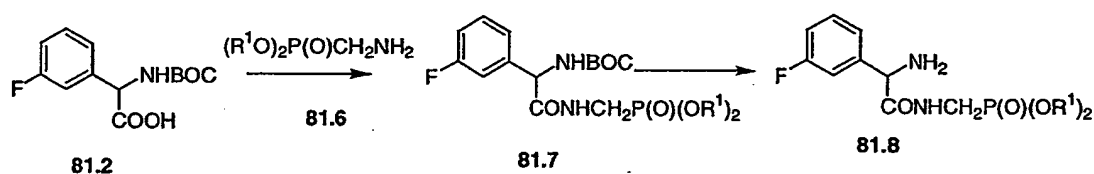**Scheme 82**

Method

Example 1

5   **Preparation of the phosphonate-containing tert. butanol derivatives 30.1.**

Schemes **83 – 86** illustrate the preparation of the tert. butanol derivatives **30.1** which are employed in the preparation of the phosphonate esters **5**.
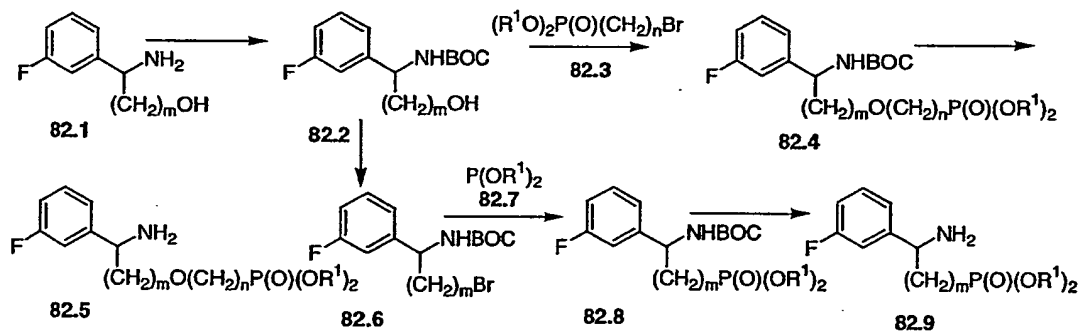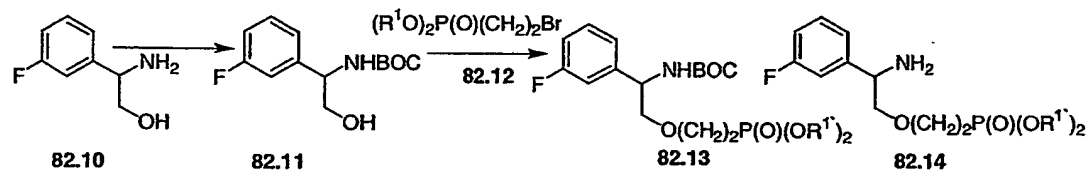
Scheme 83 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an alkylene chain. In this procedure, a bromoalkyl carbinol 83.1 is reacted with a trialkyl phosphite 83.2 in an Arbuzov reaction, to afford the phosphonate 83.3.

5   For example, 4-bromo-2-methyl-butan-2-ol 83.4 prepared as described in Bioorg. Med. Chem. Lett., 2001, 9, 525, and a trialkyl phosphite 83.2 are heated at ca. 120° to produce the phosphonate 83.5.

Using the above procedures, but employing, in place of the bromo compound 83.4 different bromo compounds 83.1, and/or different phosphites 83.2 the corresponding products 83.3 are

10   obtained.

Scheme 84 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an amide linkage. In this procedure, a carboxylic acid 84.1 is coupled with a dialkyl aminoalkyl phosphonate 84.2 to afford the amide 84.3. The reaction is

15   conducted under the conditions previously described (Scheme 1) for the preparation of amides.

For example, equimolar amounts of 3-hydroxy-3-methyl-butyric acid 84.4, (Fluka) and a dialkyl aminoethyl phosphonate 84.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted in tetrahydrofuran in the presence of dicyclohexylcarbodiimide to

20   yield the amide 84.6.

Using the above procedures, but employing, in place of the carboxylic acid 84.4 different acids 84.1, and/or different amines 84.2 the corresponding products 84.3 are obtained.

Scheme 85 depicts the preparation of tert. butanol derivatives in which the phosphonate is

25   attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted carbinol 85.1 is reacted with a dialkyl bromoalkyl phosphonate 85.2 to afford the ether, thioether or amine products 85.3. The reaction is conducted in a polar organic solvent in the presence of suitable base such as sodium hydride or cesium carbonate. For example, 4-mercapto-2-methyl-butan-2-ol 85.4 prepared as described in Bioorg. Med.

30   Chem. Lett., 1999, 9, 1715, is reacted in tetrahydrofuran containing cesium carbonate with a dialkyl bromobutyl phosphonate 85.5, the preparation of which is described in Synthesis, 1994, 9, 909, to yield the thioether 85.6.

Using the above procedures, but employing, in place of the thiol **85.4** different alcohols, thiol or amines **85.1**, and/or different bromides **85.2** the corresponding products **85.3** are obtained.

Scheme **86** depicts the preparation of tert. butanol derivatives in which the phosphonate is
5   attached by means of a nitrogen and an alkylene chain. In this procedure, a hydroxyaldehyde
86.1 is reacted with a dialkyl aminoalkyl phosphonate **86.2** under reductive amination
conditions, as described above, (Scheme **55**) to afford the amine **86.3**.
For example, 3-hydroxy-3-methyl-butyraldehyde **86.4** and a dialkyl aminoethyl phosphonate
86.5 the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted
10 together in the presence of sodium triacetoxyborohydride, to yield the amine **86.6**.
Using the above procedures, but employing, in place of the aldehyde **86.4** different aldehydes
86.1, and/or different amines **86.2** the corresponding products **86.3** are obtained.

Scheme 82

Example 2
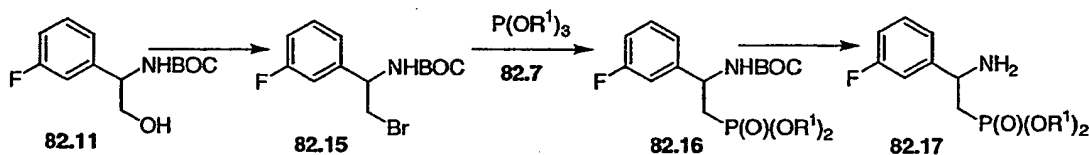
Scheme 83

Method
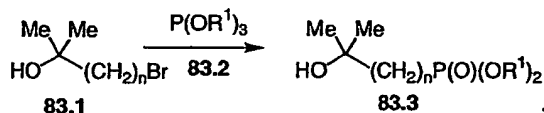
Example
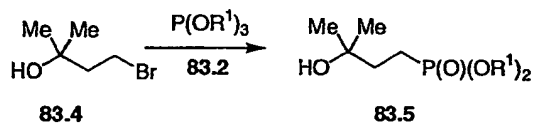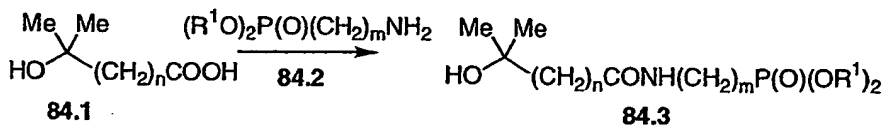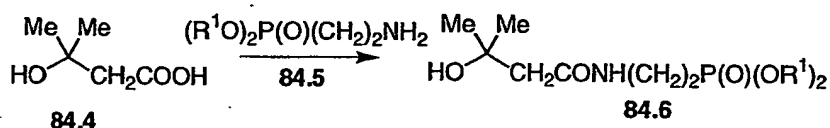
15

Scheme 84

Method

$$\underset{\textbf{84.1}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}(CH_2)_nCOOH} \quad \xrightarrow[\textbf{84.2}]{(R^1O)_2P(O)(CH_2)_mNH_2} \quad \underset{\textbf{84.3}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}(CH_2)_nCONH(CH_2)_mP(O)(OR^1)_2}$$

Example

$$\underset{\textbf{84.4}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}CH_2COOH} \quad \xrightarrow[\textbf{84.5}]{(R^1O)_2P(O)(CH_2)_2NH_2} \quad \underset{\textbf{84.6}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}CH_2CONH(CH_2)_2P(O)(OR^1)_2}$$

Scheme 85

Method

$$\underset{\textbf{85.1}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}(CH_2)_nXH} \quad \xrightarrow[\textbf{85.2}]{(R^1O)_2P(O)(CH_2)_mBr} \quad \underset{\textbf{85.3}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}(CH_2)_nX(CH_2)_mP(O)(OR^1)_2}$$

$X = O, S, NH$

Example

$$\underset{\textbf{85.4}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}SH} \quad \xrightarrow[\textbf{85.5}]{(R^1O)_2P(O)(CH_2)_4Br} \quad \underset{\textbf{85.6}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}S\diagdown\diagup\diagdown\overset{O}{\underset{OR^1}{\overset{\|}{P}}OR^1}}$$

Scheme 86

Method

$$\underset{\textbf{86.1}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}(CH_2)_nCHO} \quad \xrightarrow[\textbf{86.2}]{(R^1O)_2P(O)(CH_2)_mNH_2} \quad \underset{\textbf{86.3}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}(CH_2)_{n+1}NH(CH_2)_mP(O)(OR^1)_2}$$

Example

$$\underset{\textbf{86.4}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}CHO} \quad \xrightarrow[\textbf{86.5}]{(R^1O)_2P(O)(CH_2)_2NH_2} \quad \underset{\textbf{86.6}}{\underset{HO}{\overset{Me\diagup Me}{\diagdown}}\diagdown\underset{H}{N}\diagdown\overset{O}{\underset{OR^1}{\overset{\|}{P}}OR^1}}$$
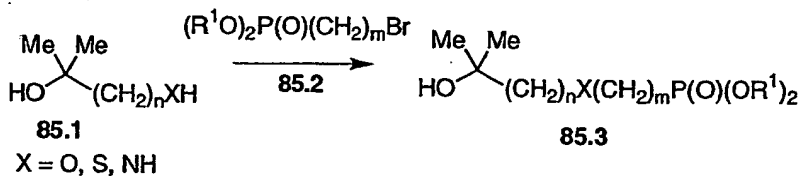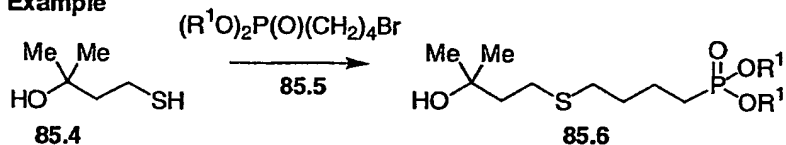
5   **Preparation of the phosphonate-containing benzyl carbamates 43.4.**

Schemes **87 - 91** illustrate methods for the preparation of the benzyl carbamates **43.4** which

are employed in the preparation of the phosphonate esters **9**. The benzyl alcohols are obtained

by reduction of the corresponding benzaldehydes, the preparation of which is described in Schemes **87 - 90.**

5   Scheme **87** illustrates the preparation of benzaldehyde phosphonates **87.3** in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde **87.1** is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate **87.2**, under reductive amination conditions, as described above in Scheme **55**, to yield the phosphonate product **87.3.**

For example, benzene-1,3-dialdehyde **87.4** is reacted with a dialkyl aminopropyl phosphonate

10   **87.5,** (Acros) and sodium triacetoxyborohydride, to afford the product **87.6.**
Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde **87.4,** different benzene dialdehydes **87.1,** and/or different phosphonates **87.2,** the corresponding products **87.3** are obtained.

15   Scheme **88** illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated car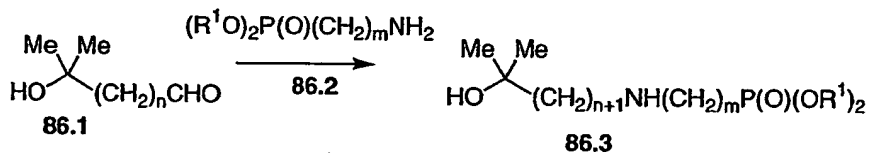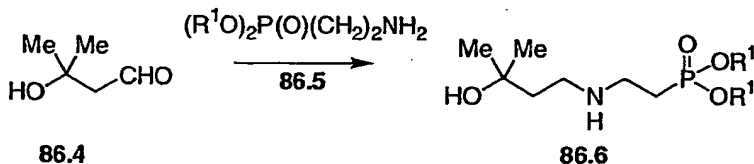bon chain. In this procedure, a bromobenzaldehyde **88.1** is coupled, as described above, with a dialkyl alkenylphosphonate **88.2,** to afford the alkenyl phosphonate **88.3.** Optionally, the product is reduced to afford the saturated phosphonate ester **88.4.** Alternatively, the bromobenzaldehyde

20   is coupled, as described above, with a dialkyl phosphite **88.5** to afford the formylphenylphosphonate **88.6.**
For example, as shown in Example 1, 3-bromobenzaldehyde **88.7** is coupled with a dialkyl propenylphosphonate **88.8** (Aldrich) to afford the propenyl product **88.9.** Optionally, the product is reduced, for example by the use of diimide, to yield the propyl phosphonate **88.10.**

25   Using the above procedures, but employing, in place of 3-bromobenzaldehyde **88.7,** different bromobenzaldehydes **88.1,** and/or different alkenyl phosphonates **88.2,** the corresponding products **88.3** and **88.4** are obtained.
Alternatively, as shown in Example 2, 4-bromobenzaldehyde is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **88.5** to afford the 4-formylphenyl phosphonate

30   product **88.12.**
Using the above procedures, but employing, in place of 4-bromobenzaldehyde **88.11,** different bromobenzaldehydes **88.1,** the corresponding products **88.6** are obtained.

Scheme **89** illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or

5   alkylamine **89.1** is reacted with a an equimolar amount of a dialkyl haloalkyl phosphonate **89.2**, to afford the phenoxy, phenylthio or phenylamino phosphonate product **89.3**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **89.1**. In cases in which Y is O, a strong base such as sodium hydride or lithium

10   hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **89.4**, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl iodomethyl phosphonate **89.5**, (Lancaster) to give the ether product **89.6**.

15   Using the above procedures, but employing, in place of the carbinol **89.4**, different carbinols, thiols or amines **89.1**, and/or different haloalkyl phosphonates **89.2**, the corresponding products **89.3** are obtained.

Scheme **90** illustrates the preparation of formylphenyl phosphonates in which the phosphonate

20   group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid **90.1** is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, **90.2**, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to afford diaryl compounds is described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p.

25   218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product **90.3** is then coupled, as described above (Scheme **50**) with a dialkyl phosphite **90.4** to afford the phosphonate **90.5**. For example, 4-formylbenzeneboronic acid **90.6** is coupled with 2,5-dibromothiophene **90.7** to yield the phenylthiophene product **90.8**. This compound is then coupled with the dialkyl

30   phosphite **90.4** to afford the thienyl phosphonate **90.9**.

Using the above procedures, but employing, in place of dibromothiophene **90.7**, different

dibromoarenes **90.2**, and/or different formylphenyl boronates **90.1**, the corresponding products

90.5 are obtained.

5   Scheme **91** illustrates the preparation of the benzyl carbamates **43.4** which are employed in the

preparation of the phosphonate esters **9**. In this procedure, the substituted benzaldehydes **91.1**,

prepared as shown in Schemes **87 – 90**, are converted into the corresponding benzyl alcohols

91.2. The reduction of aldehydes to afford alcohols is described in Comprehensive Organic

Transformations, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the

10   use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy

hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted

with the aminoester **91.3** to afford the carbamate **91.4**. The reaction is performed under the

conditions described below, Scheme **98**. For example, the benzyl alcohol is reacted with

carbonyldiimidazole to produce an intermediate benzyloxycarbonyl imidazole, and the

15   intermediate is reacted with the aminoester **91.3** to afford the carbamate **91.4**. The methyl

ester is then hydrolyzed to yield the carboxylic acid **43.4**.

Scheme 87
Method
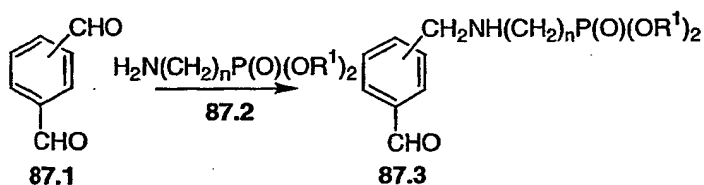
Example
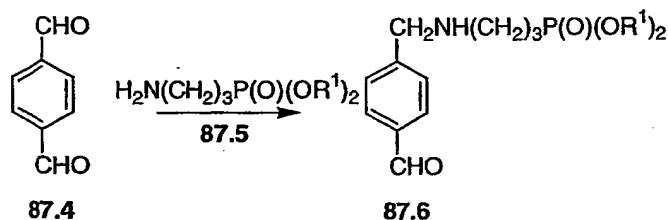
Scheme 88

Method
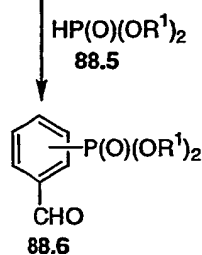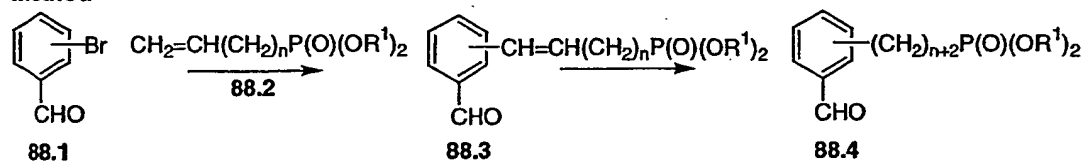
Example 1
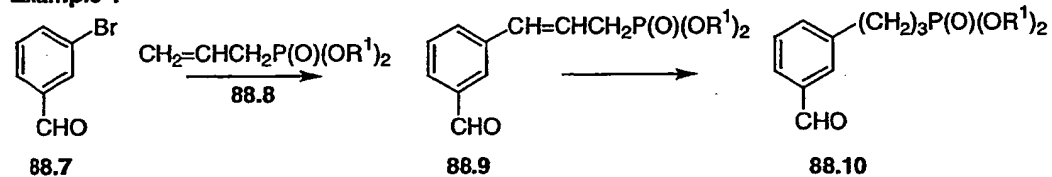
Example 2

Scheme 89

Method

X, Y = O, S, NH

89.1

89.3
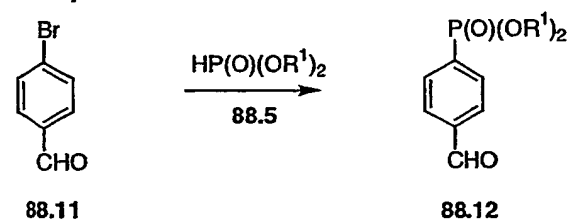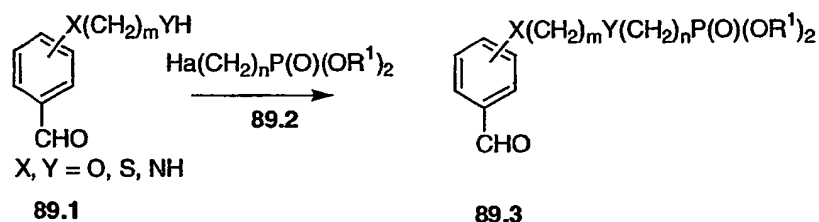
Example

Scheme 90

Method
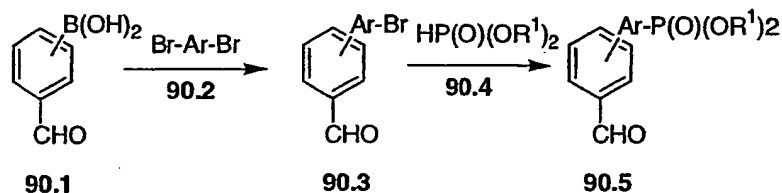
90.1 → 90.3 → 90.5

Example

90.6 → 90.8 → 90.9

Scheme 91

91.1 → 91.2 → 91.4 → 43.4
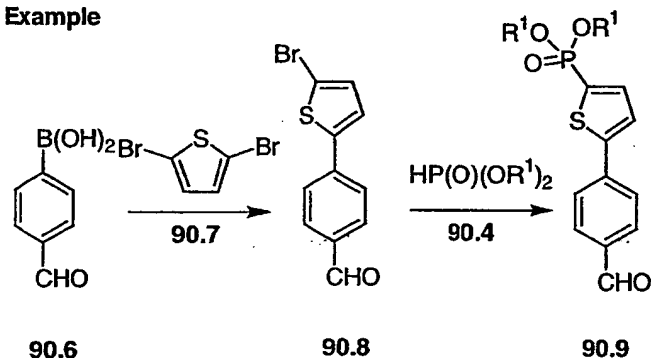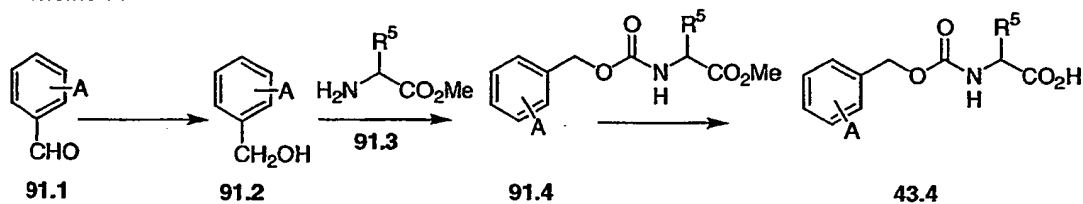
Preparation of phosphonate-containing benzenesulfonyl chlorides 20.2.

Schemes **92 - 97** illustrate methods for the preparation of the sulfonyl chlorides **20.2** which are employed in the preparation of the phosphonate esters **4**. Sulfonic acids and/or sulfonyl halides are obtained by oxidation of the corresponding thiols, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 813, and in Tet. 1965, 21, 2271. For example, the phosphonate-containing thiols which are prepared according to Schemes **63 - 72** are transformed into the corresponding sulfonic acids by oxidation with bromine in aqueous organic solution, as described in J. Am. Chem. Soc., 59, 811, 1937, or by oxidation with hydrogen peroxide, as described in Rec. Trav. Chim., 54, 205, 1935, or by reaction with

oxygen in alkaline solution, as described in Tet. Let., 1963, 1131, or by the use of potassium superoxide, as described in Aust. J. Chem., 1984, 37, 2231. Schemes **92- 96** describe the preparation of phosphonate-substituted benzenesulfonic acids; Scheme **97** describes the conversion of the sulfonic acids into the corresponding sulfonyl chlorides. Alternatively, the

5   intermediate thiols, when propduced, can be directly converted to the sulfonyl chloride as described in Scheme **97a**

Scheme **92** depicts the preparation of variously substituted benzenesulfonic acids in which the phosphonate group is directly attached to the benzene ring. In this procedure, a bromo-

10   substituted benzenethiol **92.1** is protected, as previously described. The protected product **92.2** is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **92.3**, to give the corresponding phosphonate **92.4**. The thiol group is then deprotected to afford the thiol **92.5**, and this compound is oxidized to afford the sulfonic acid **92.6**.

For example, 4-bromobenzenethiol **92.7** is converted into the S-adamantyl derivative **92.8**, by

15   reaction with 1-adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The product is then reacted with a dialkyl phosphite and a palladium catalyst, as described previously, to yield the phosphonate **92.9**. The adamantyl group is then removed by reaction with mercuric acetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, to give the thiol **92.10**. The product is then reacted with bromine in aqueous

20   solution to prepare the sulfonic acid **92.11**.

Using the above procedures, but employing, in place of the thiol **92.7**, different thiols **92.1**, and/or different dialkyl phosphites **92.3**, the corresponding products **92.6** are obtained.

Scheme **93** illustrates the preparation of amino-substituted benzenesulfonic acids in which the

25   phosphonate group is attached by means of an alkoxy group. In this procedure, a hydroxy amino-substituted benzenesulfonic acid **93.1** is reacted with a dialkyl bromoalkyl phosphonate **93.2** to afford the ether **93.3**. The reaction is performed in a polar solvent such as dimethylformamide in the presence of a base such as potassium carbonate. The yield of the product **93.3** is increased by treatment of the crude reaction product with dilute aqueous base,

30   so as to hydrolyze any sulfonic esters which are produced.

For example, 3-amino-4-hydroxybenzenesulfonic acid **93.4** (Fluka) is reacted with a dialkyl bromopropyl phosphonate **93.5** prepared as described in J. Am. Chem. Soc., 2000, 122, 1554,

in dimethylformamide containing potassium carbonate, followed by the addition of water, to produce the ether **93.6**.

Using the above procedures, but employing, in place of the phenol **93.4**, different phenols **93.1**, and/or different phosphonates **93.2**, the corresponding products **93.3** are obtained.

5

Scheme **94** illustrates the preparation of methoxyl-substituted benzenesulfonic acids in which the phosphonate group is attached by means of an amide group. In this procedure, a methoxy amino-substituted benzenesulfonic acid **94.1** is reacted, as described previously for the preparation of amides, with a dialkyl carboxyalkyl phosphonate **94.2** to produce the amide

10 **94.3**.

For example, 3-amino-4-methoxybenzenesulfonic acid **94.4**, (Acros) is reacted in dimethylformamide solution with a dialkyl phosphonoacetic acid **94.2** (Aldrich) and dicyclohexyl carbodiimide, to produce the amide **94.6**.

Using the above procedures, but employing, in place of the amine **94.4**, different amines **94.1**,

15 and/or different phosphonates **94.2**, the corresponding products **94.3** are obtained.

Scheme **95** illustrates the preparation of substituted benzenesulfonic acids in which the phosphonate group is attached by means of a saturated or unsaturated alkylene group. In this procedure, a halo-substituted benzenesulfonic acid **95.1** is coupled, in a palladium catalyzed

20 Heck reaction with a dialkyl alkenyl phosphonate **95.2** to afford the phosphonate **95.3**. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to give the saturated analog **95.4**.

For example, 4-amino-3-chlorobenzenesulfonic aid **95.5** (Acros) is reacted in N-methylpyrrolidinone solution at 80° with a dialkyl vinylphosphonate **95.6** (Aldrich), palladium

25 (II) chloride bis(acetonitrile), sodium acetate and tetraphenylphosphonium chloride, as described in Ang. Chem. Int. Ed. Engl., 37, 481, 1998, to produce the olefinic product **95.7**. Catalytic hydrogenation using a 5% palladium on carbon catalyst then affords the saturated analog **95.8**.

Using the above procedures, but employing, in place of the chloro compound **95.5**, different

30 chlorides **95.1**, and/or different phosphonates **95.2**, the corresponding products **95.3** and **95.4** are obtained.

Scheme **96** depicts the preparation of benzenesulfonic acids in which the phosphonate group is attached by means of an amide linkage. In this procedure, an amino carboxy substituted benzene thiol **96.1** is coupled with a dialkyl aminoalkyl phosphonate **96.2** to produce the amide **96.3**. The product is then oxidized, as described above, to afford the corresponding

5   sulfonic acid **96.4**.

For example, 2-amino-5-mercaptobenzoic acid **96.5**, prepared as described in Pharmazie, 1973, 28, 433, is reacted with a dialkyl aminoethyl phosphonate **96.6** and dicyclohexyl carbodiimide, to prepare the amide **96.7**. The product is then oxidized with aqueous hydrogen peroxide to yield the sulfonic acid **96.8**.

10   Using the above procedures, but employing, in place of the carboxylic acid **96.5**, different acids **96.1**, and/or different phosphonates **96.2**, the corresponding products **96.4** are obtained.

Scheme **97** illustrates the conversion of benzenesulfonic acids into the corresponding sulfonyl chlorides. The conversion of sulfonic acids into sulfonyl chlorides is described in Synthetic

15   Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 821. The transformation is effected by the use of reagents such as thionyl chloride or phosphorus pentachloride.

For example, as shown in Scheme **97**, the variously substituted phosphonate-containing benzenesulfonic acids **97.1**, prepared as described above, are treated with thionyl chloride, oxalyl chloride, phosphorus pentachloride, phosphorus oxychloride and the like to prepare the

20   corresponding sulfonyl chlorides **97.2**.

Scheme **97a** illustrates the conversion of thiols into the corresponding sulfonyl chlorides which can be applied to any of the thiol intermediates in Schemes **92-96**. The thiol is oxidized as described in Synthesis 1987, 4, 409 or J. Med. Chem. 1980, 12, 1376 to afford the sulfonyl

25   chloride directly. For example, treatment of protected thiol **97a.1**, prepared from **96.7** using standard protecting groups for amines as described in Greene and Wuts, third edition, ch 7, with HCl and chlorine affords the sulfonyl chloride **97a.2**. Alternatively treatment of **92.10** with the same conditions gives the sulfonyl chloride **97a.3**.

Scheme 92

Method
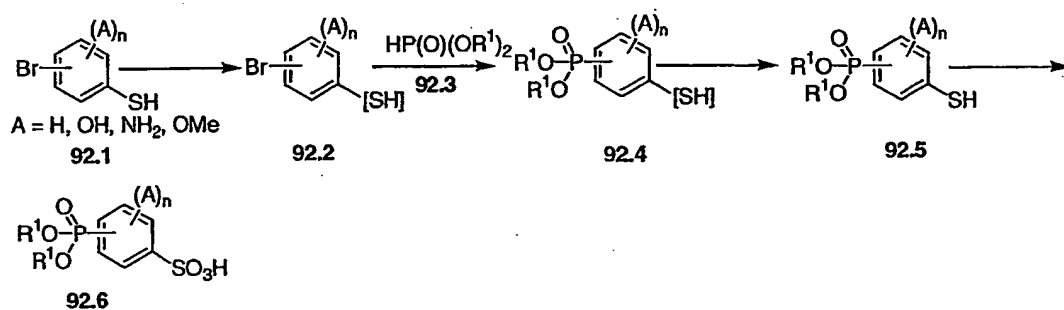
Example

Scheme 93

Method

R = NH₂, H, OMe
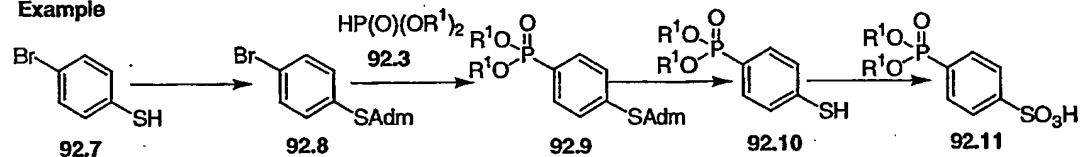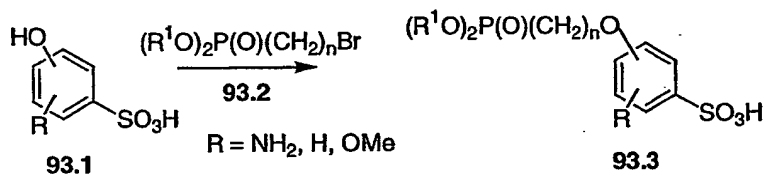
Example

Scheme 94

Method

R = OMe, NH₂, H
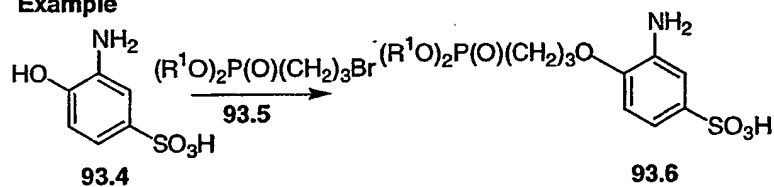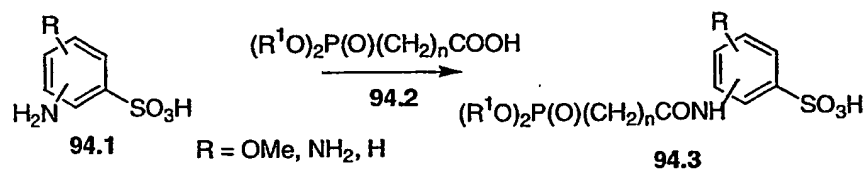
Example

Scheme 95

Method

A = H, OMe, NH_2

95.1

Example

Scheme 96

Method

A = H, OMe, Ha

96.1

Example

5

Scheme 97

$(R^1O)_2P(O)link$—[ring with $(A)_n$]—SO_3H $\longrightarrow$ $(R^1O)_2P(O)link$—[ring with $(A)_n$]—SO_2Cl

A = H, Ha, MeO, NH_2 etc

97.1   **97.2**

Scheme 97a

$(R^1O)_2P(O)link$—[ring with $(A)_n$]—SH $\longrightarrow$ $(R^1O)_2P(O)link$—[ring with $(A)_n$]—SO_2Cl

A = H, Ha, MeO, NH_2 etc

97a.1   **97.2**

Example

$(R^1O)_2P(O)(CH_2)_2NH$—[ring with H_2N and SH, C=O] $\longrightarrow$ $(R^1O)_2P(O)(CH_2)_2NH$—[ring with H_2N and SO_2Cl, C=O]

97a.1   **97a.2**

[phosphonate ring with R^1O, R^1O, P=O and SH] $\longrightarrow$ [phosphonate ring with R^1O, R^1O, P=O and SO_2Cl]

92.10   **97a.3**
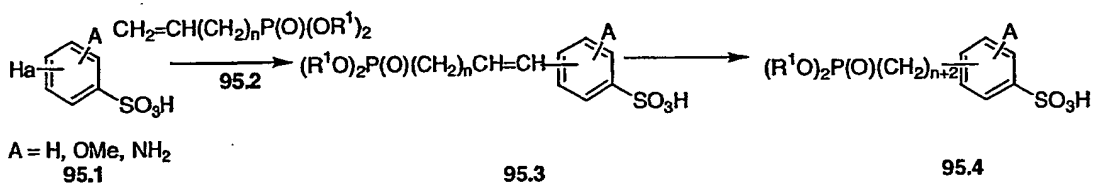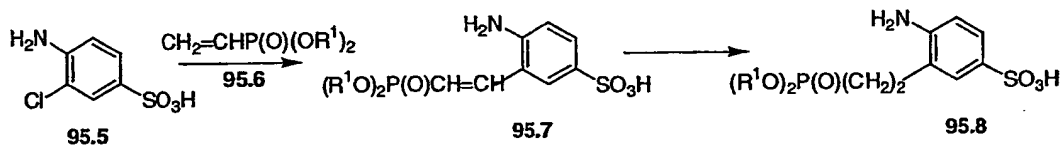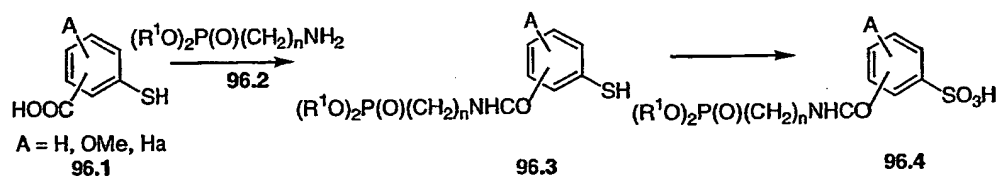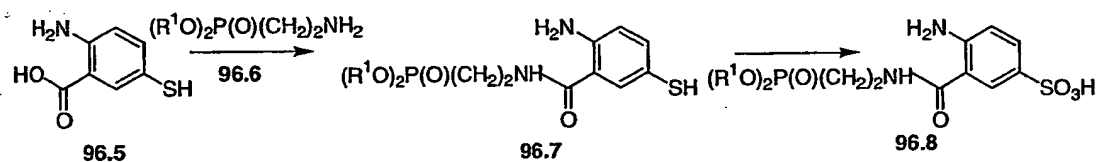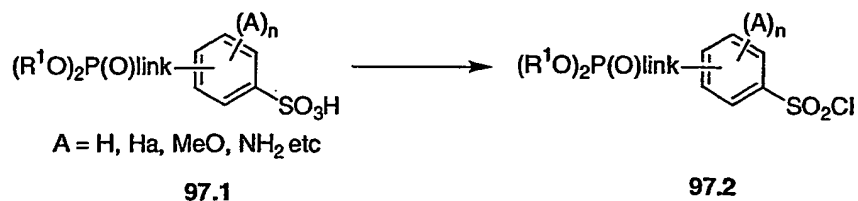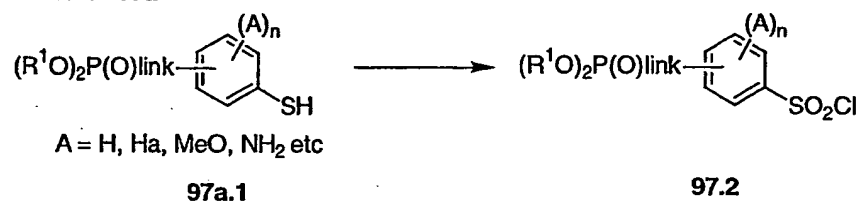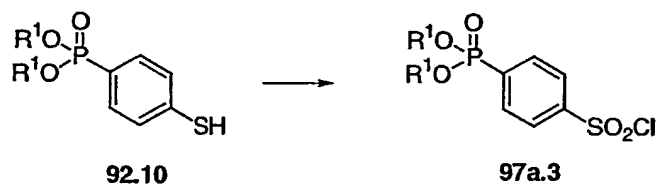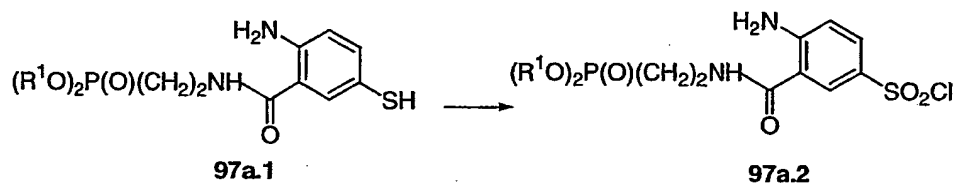
5   **Preparation of carbamates.**

The phosphonate esters **1 - 4** in which R^4 is formally derived from the carboxylic acids shown in Chart 5c, and the phosphonate esters **5** and **9** contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A.

10   R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 98 illustrates various methods by which the carbamate linkage is synthesized. As

shown in Scheme 98, in the general reaction generating carbamates, a carbinol **98.1**, is

converted into the activated derivative **98.2** in which Lv is a leaving group such as halo,

imidazolyl, benztriazolyl and the like, as described below. The activated derivative **98.2** is then

5   reacted with an amine **98.3**, to afford the carbamate product **98.4**. Examples **1 – 7** in Scheme

98 depict methods by which the general reaction is effected. Examples **8 - 10** illustrate

alternative methods for the preparation of carbamates.

Scheme 98, Example 1 illustrates the preparation of carbamates employing a chloroformyl

derivative of the carbinol **98.1**. In this procedure, the carbinol is reacted with phosgene, in an

10   inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or

with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn.

Coll. Vol. 6, 715, 1988, to afford the chloroformate **98.6**. The latter compound is then reacted

with the amine component **98.3**, in the presence of an organic or inorganic base, to afford the

carbamate **98.7**. For example, the chloroformyl compound **98.6** is reacted with the amine **98.3**

15   in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium

hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **98.7**.

Alternatively, the reaction is performed in dichloromethane in the presence of an organic base

such as diisopropylethylamine or dimethylaminopyridine.

Scheme 98, Example 2 depicts the reaction of the chloroformate compound **98.6** with

20   imidazole to produce the imidazolide **98.8**. The imidazolide product is then reacted with the

amine **98.3** to yield the carbamate **98.7**. The preparation of the imidazolide is performed in an

aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is

conducted in a similar solvent at ambient temperature, optionally in the presence of a base

such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

25   Scheme 98 Example 3, depicts the reaction of the chloroformate **98.6** with an activated

hydroxyl compound R"OH, to yield the mixed carbonate ester **98.10**. The reaction is

conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a

base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected

from the group of compounds **98.19 - 98.24** shown in Scheme 98, and similar compounds. For

30   example, if the component R"OH is hydroxybenztriazole **98.19**, N-hydroxysuccinimide **98.20**,

or pentachlorophenol, **98.21**, the mixed carbonate **98.10** is obtained by the reaction of the

chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which
the component R"OH is pentafluorophenol 98.22 or 2-hydroxypyridine 98.23 is performed in
an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and
Chem. Ber. 118, 468, 1985.

5   Scheme 98 Example 4 illustrates the preparation of carbamates in which an
alkyloxycarbonylimidazole 98.8 is employed. In this procedure, a carbinol 98.5 is reacted with
an equimolar amount of carbonyl diimidazole 98.11 to prepare the intermediate 98.8. The
reaction is conducted in an aprotic organic solvent such as dichloromethane or
tetrahydrofuran. The acyloxyimidazole 98.8 is then reacted with an equimolar amount of the

10 amine R'NH$_2$ to afford the carbamate 98.7. The reaction is performed in an aprotic organic
solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the
carbamate 98.7.

Scheme 98, Example 5 illustrates the preparation of carbamates by means of an intermediate
alkoxycarbonylbenztriazole 98.13. In this procedure, a carbinol ROH is reacted at ambient

15 temperature with an equimolar amount of benztriazole carbonyl chloride 98.12, to afford the
alkoxycarbonyl product 98.13. The reaction is performed in an organic solvent such as
benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as
described in Syn., 1977, 704. The product is then reacted with the amine R'NH$_2$ to afford the
carbamate 98.7. The reaction is conducted in toluene or ethanol, at from ambient temperature

20 to about 80° as described in Syn., 1977, 704.

Scheme 98, Example 6 illustrates the preparation of carbamates in which a carbonate
(R"O)$_2$CO, 98.14, is reacted with a carbinol 98.5 to afford the intermediate alkyloxycarbonyl
intermediate 98.15. The latter reagent is then reacted with the amine R'NH$_2$ to afford the
carbamate 98.7. The procedure in which the reagent 98.15 is derived from

25 hydroxybenztriazole 98.19 is described in Synthesis, 1993, 908; the procedure in which the
reagent 98.15 is derived from N-hydroxysuccinimide 98.20 is described in Tet. Lett., 1992,
2781; the procedure in which the reagent 98.15 is derived from 2-hydroxypyridine 98.23 is
described in Tet. Lett., 1991, 4251; the procedure in which the reagent 98.15 is derived from
4-nitrophenol 98.24 is described in Syn. 1993, 199. The reaction between equimolar amounts

30 of the carbinol ROH and the carbonate 98.14 is conducted in an inert organic solvent at
ambient temperature.

Scheme **98**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides
98.16. In this procedure, an alkyl chloroformate **98.6** is reacted with an azide, for example
sodium azide, to afford the alkoxycarbonyl azide **98.16**. The latter compound is then reacted
with an equimolar amount of the amine R'NH$_2$ to afford the carbamate **98.7**. The reaction is

5   conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for
example as described in Syn., 1982, 404.

Scheme **98**, Example **8** illustrates the preparation of carbamates by means of the reaction
between a carbinol ROH and the chloroformyl derivative of an amine **98.17**. In this procedure,
which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953,

10   p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as
acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **98.7**.
Scheme **98**, Example **9** illustrates the preparation of carbamates by means of the reaction
between a carbinol ROH and an isocyanate **98.18**. In this procedure, which is described in
Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants

15   are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane
and the like, to afford the carbamate **98.7**.

Scheme **98**, Example **10** illustrates the preparation of carbamates by means of the reaction
between a carbinol ROH and an amine R'NH$_2$. In this procedure, which is described in Chem.
Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic

20   solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and
selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford
the carbamate **98.7**.

Scheme 98

General reaction

ROH ——————→ ROCOLv —R'NH₂→ ROCONHR'

98.1   98.2   98.3   98.4

Examples

(1) ROH ——————→ ROCOCl —R'NH₂ 98.3→ ROCONHR'

98.5   98.6   98.7

(2) ROH ——————→ ROCOCl ——→ (98.8) —R'NH₂→ ROCONHR' 98.7

98.5   98.6   98.8   98.3

(3) ROH ——————→ ROCOCl —R"OH→ ROCOOR" —R'NH₂→ ROCONHR'

98.5   98.6   98.9   98.10   98.3   98.7

(4) ROH —98.11→ (98.8) —R'NH₂→ ROCONHR'

98.5   98.8   98.3   98.7

(5) ROH ——————→ (98.13) —R'NH₂→ ROCONHR'

98.5   98.12   98.13   98.3   98.7

(6) ROH —(R"O₂)C=O→ ROCOR" —R'NH₂→ ROCONHR'

98.5   98.14   98.15   98.3   98.7

(7) ROH ——————→ ROCOCl ——→ ROCON₃ —R'NH₂→ ROCONHR'

98.5   98.6   98.16   98.3   98.7

(8) ROH —R'NHCOCl→ ROCONHR'

98.5   98.17   98.7

(9) ROH —R'NCO→ ROCONHR'

98.5   98.18   98.7

(10) ROH —R'NH₂→ ROCONHR'

98.5   98.3   98.7

R"OH =   98.19   98.20   98.21   98.22   98.23   98.24

Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1 - 97** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Charts 1 and 2,

5   may be the same or different. The R^1 groups attached to the phosphonate esters **1 - 13**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **99**. The group R in Scheme **99** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1 - 13** or in precursors thereto. The R^1 group may be changed, using

10   the procedures described below, either in the precursor compounds, or in the esters **1 - 13**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **99.1** into the corresponding phosphonate monoester

15   **99.2** (Scheme **99**, Reaction 1) is accomplished by a number of methods. For example, the ester **99.1** in which R^1 is an aralkyl group such as benzyl, is converted into the monoester compound **99.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the

20   diester **99.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **99.2** is effected by treatment of the ester **99.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **99.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters **99.2** in which R^1 is alkyl by hydrogenation,

25   for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, are converted into the monoester **99.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl

30   carboxylates.

The conversion of a phosphonate diester **99.1** or a phosphonate monoester **99.2** into the

corresponding phosphonic acid **99.3** (Scheme **99**, Reactions 2 and 3) is effected by reaction of

the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem.

Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example,

5   dichloromethane, optionally in the presence of a silylating agent such as

bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **99.2**

in which R^1 is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **99.3**

by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an

ethereal solvent such as dioxan. A phosphonate monoester **99.2** in which R^1 is alkenyl such as,

10 for example, allyl, is converted into the phosphonic acid **99.3** by reaction with Wilkinson's

catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous

ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985.

Palladium catalyzed hydrogenolysis of phosphonate esters **99.1** in which R^1 is benzyl is

described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate

15 esters **99.1** in which R^1 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **99.2** into a phosphonate diester **99.1** (Scheme **99**,

Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as

chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **99.2** is

reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable

20 coupling agents are those employed for the preparation of carboxylate esters, and include a

carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably

conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-

yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the

reaction is performed in a polar solvent such as dimethylformamide, in the presence of a

25 tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the

reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine

such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **99.2**

to the diester **99.1** is effected by the use of the Mitsonobu reaction, as described above,

Scheme **49**. The substrate is reacted with the hydroxy compound R^1OH, in the presence of

30 diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the

phosphonate monoester **99.2** is transformed into the phosphonate diester **99.1**, in which the

introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in

which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic

solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium

carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate

diester in a two step procedure. In the first step, the phosphonate monoester **99.2** is

5   transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl

chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L.

Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted

with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford

the phosphonate diester **99.1**.

10   A phosphonic acid R-link-$P(O)(OH)_2$ is transformed into a phosphonate monoester

$RP(O)(OR^1)(OH)$ (Scheme **99**, Reaction **5**) by means of the methods described above of for

the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **99.1**, except that only one molar

proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **99.3** is transformed into a phosphonate diester R-link-

15   $P(O)(OR^1)_2$ **99.1** (Scheme **99**, Reaction **6**) by a coupling reaction with the hydroxy compound

R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and

triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

Alternatively, phosphonic acids **99.3** are transformed into phosphonic esters **99.1** in which R^1

is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in

20   pyridine at ca 70°. Alternatively, phosphonic acids **99.3** are transformed into phosphonic esters

99.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted

with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux

temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester

99.1.

Scheme 99
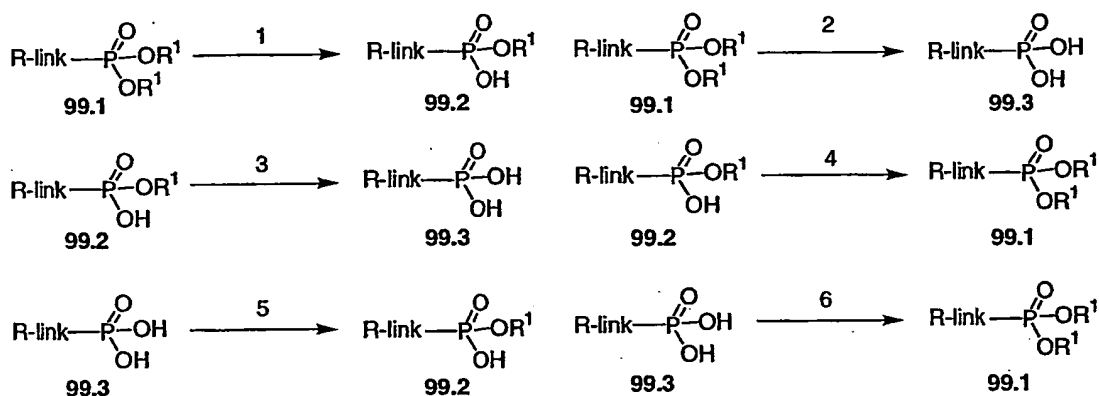
General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes 47 - 97) are, with appropriate modifications known to one skilled in the art, transferable to different

5   chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into hydroxymethyl benzoic acids, (Schemes 47 - 51) are applicable to the introduction of phosphonate moieties into quinolines, thiophenols, isobutylamines, cyclopentylamines, tert. butanols, benzyl alcohols, phenylalanines, benzylamines and benzenesulfonic acids, and the methods described for the introduction of phosphonate moieties

10   into the above-named substrates (Schemes 52 - 97) are applicable to the introduction of phosphonate moieties into hydroxymethyl benzoic acid substrates.

Preparation of phosphonate intermediates 11 - 13 with phosphonate moieties incorporated into the R^2, R^3 or R^4 groups.

15

The chemical transformations described in Schemes 1 - 99 illustrate the preparation of compounds 1 - 10 in which the phosphonate ester moiety is attached to the substructures listed above. The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to

20   those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^4COOH, R^3Cl, R^2NH_2. The resultant phosphonate-containing analogs, designated as $R^{4a}COOH$, $R^{3a}Cl$ and NH_2R^{2a} are then, using the procedures described above, employed in the preparation of the compounds 11, 12 and 13. The procedures required for the

utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2NH_2, R^3Cl and R^4COOH.

5   KNI-like phosphonate protease inhibitors (KNILPPI)

Preparation of the intermediate phosphonate esters 1-12.

The structures of the intermediate phosphonate esters **1** to **12** and the structures for the component groups R^1, R^2, R^3, R^7, R^9, X and Y of this invention are shown in Charts **1** and **2**.

10   The structures of the R^8COOH components are shown in Charts **3a**, **3b** and **3c**.

The structures of the $R^{10}R^{11}NH$ and R^4R^5NH components are shown in Charts **4a**, and **4b** respectively. The structures of the R^6XCH_2 groups are shown in Chart **5**. Specific stereoisomers of some of the structures are shown in Charts **1** - **5**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **12**. Subsequent chemical modifications to

15   the compounds **1** to **12**, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds **1** to **12** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **6** and **7** illustrate examples of the linking groups present in the

20   structures **1** - **12**.

Schemes **1** - **103** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **10**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **11** and **12**, in which the phosphonate moiety is incorporated into the groups R^8COOH and $R^{10}R^{11}NH$, is also described below.

25

Chart 1
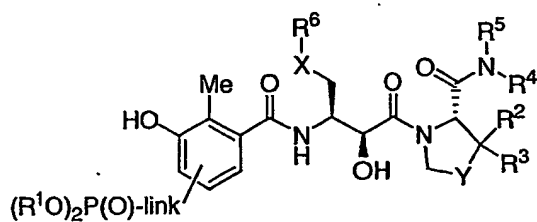
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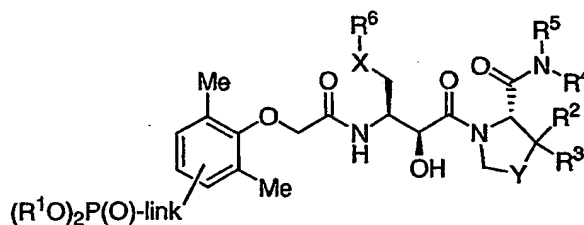
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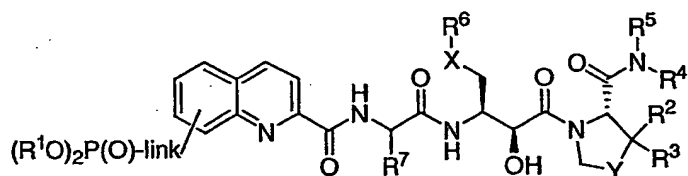
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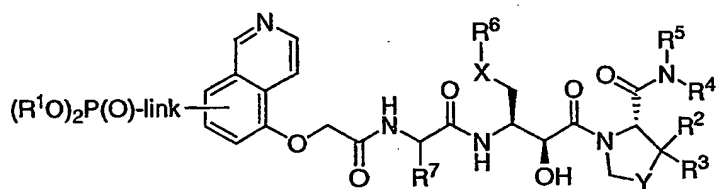
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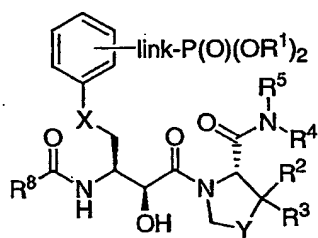
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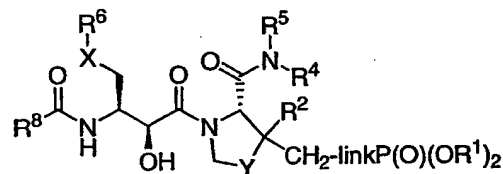
6

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^2, R^3 = H,H; H, methyl; methyl, methyl; H, Cl

R^7 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

X = S or direct bond

Y = S, CH_2

Chart 2

7

8

9

10

11
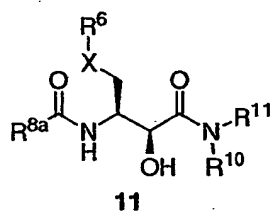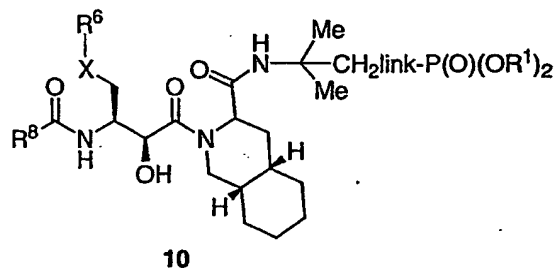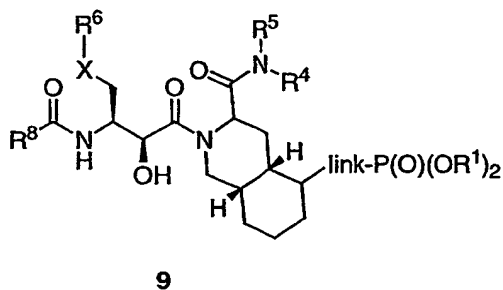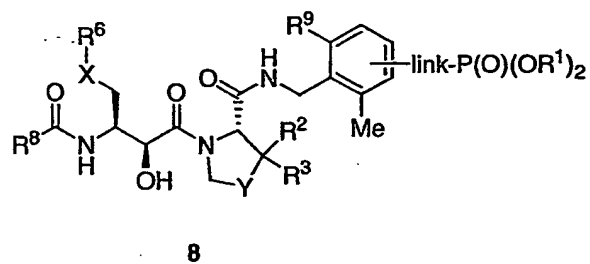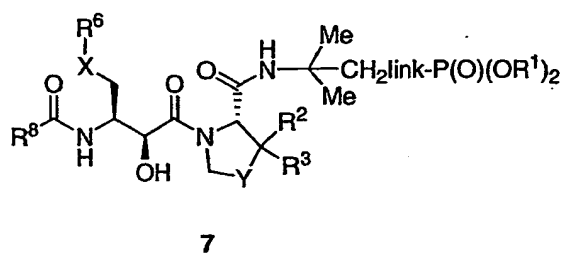
R⁸ᵃ = phosphonate-containing R^8

12
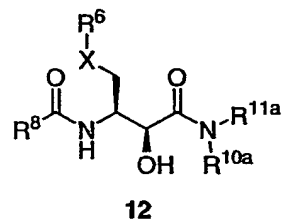
R^{10a}, R^{11a} = phosphonate-containing R^{10} or R^{11}

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^2, R^3 = H,H; H, methyl; methyl, methyl; H, Cl.

R^9 = H, methyl

X = S or direct bond

Y = S, CH_2

Chart 3a Structures of the R^8COOH components
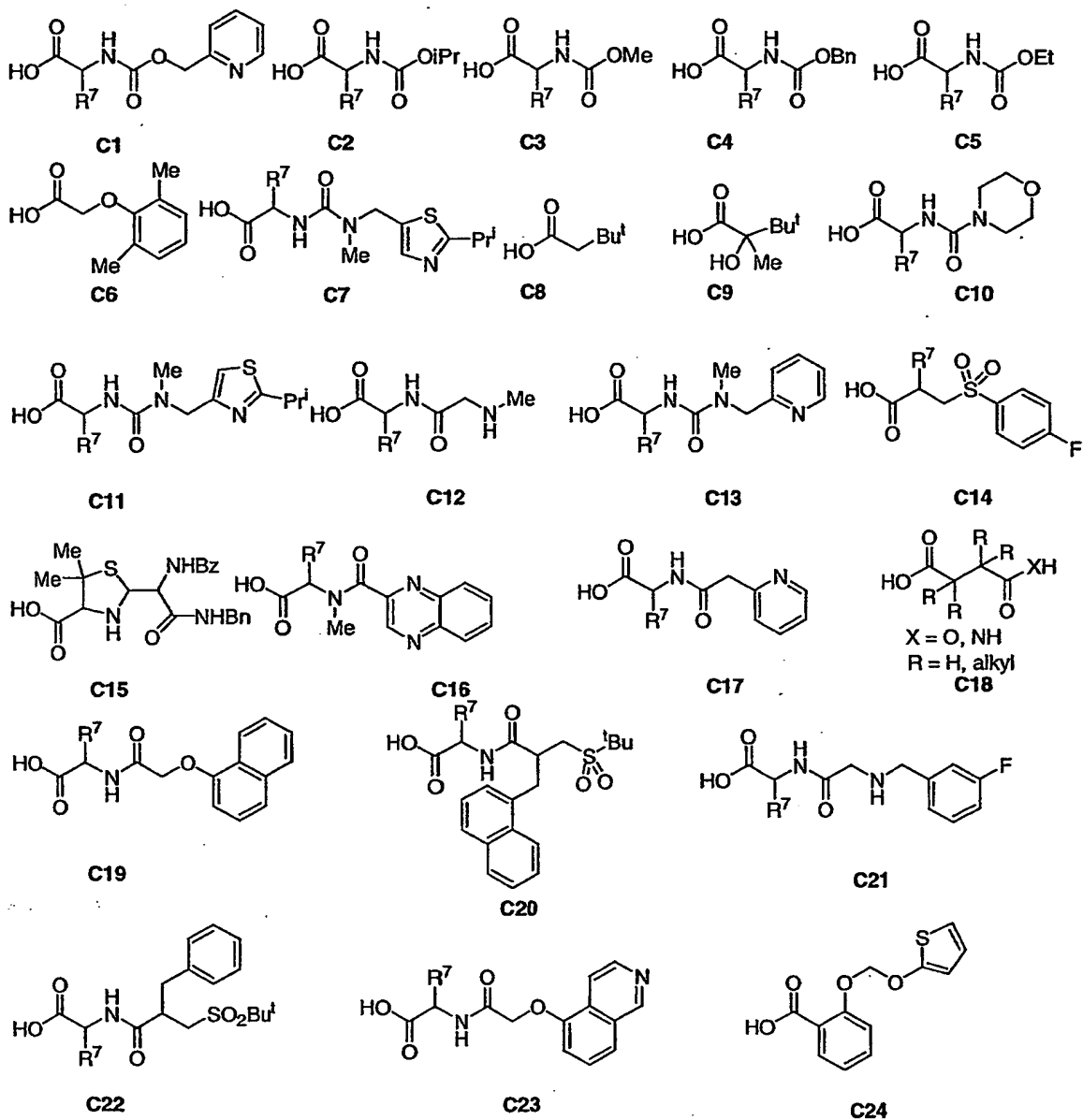
C1   C2   C3   C4   C5

C6   C7   C8   C9   C10

C11   C12   C13   C14

C15   C16   C17   X = O, NH   R = H, alkyl   C18

C19   C20   C21

C22   C23   C24

R^7 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 3b Structures of the R⁸COOH components
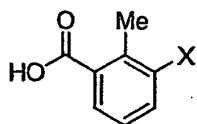
C25
X = OH, NH₂
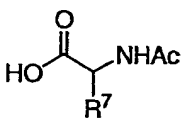
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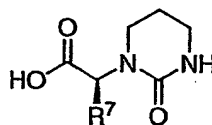
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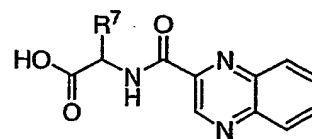
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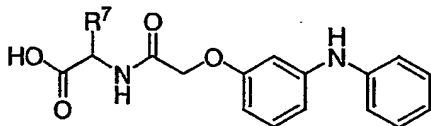
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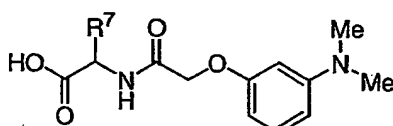
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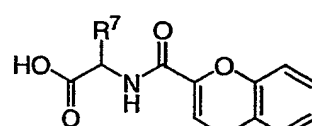
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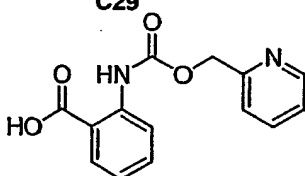
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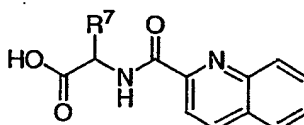
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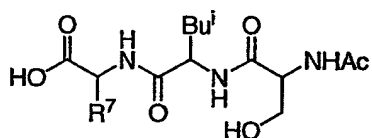
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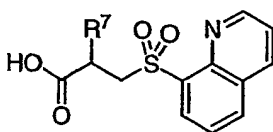
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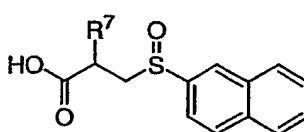
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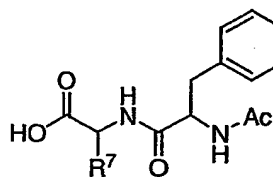
C37

R⁷ = alkyl, CH₂SO₂CH₃,C(CH₃)₂SO₂CH₃,CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 3c Structures of the R⁸COOH components
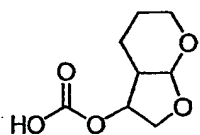
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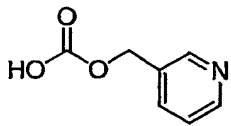
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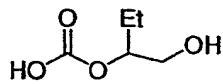
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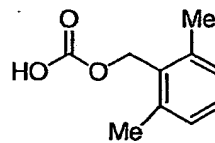
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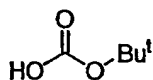
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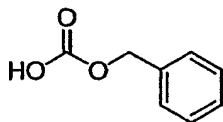
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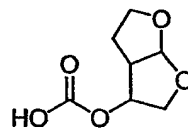
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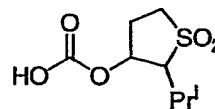
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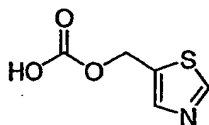
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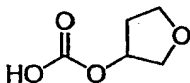
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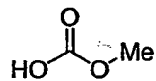
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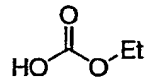
C49

Chart 4a Structures of the $R^{10}R^{11}NH$ components
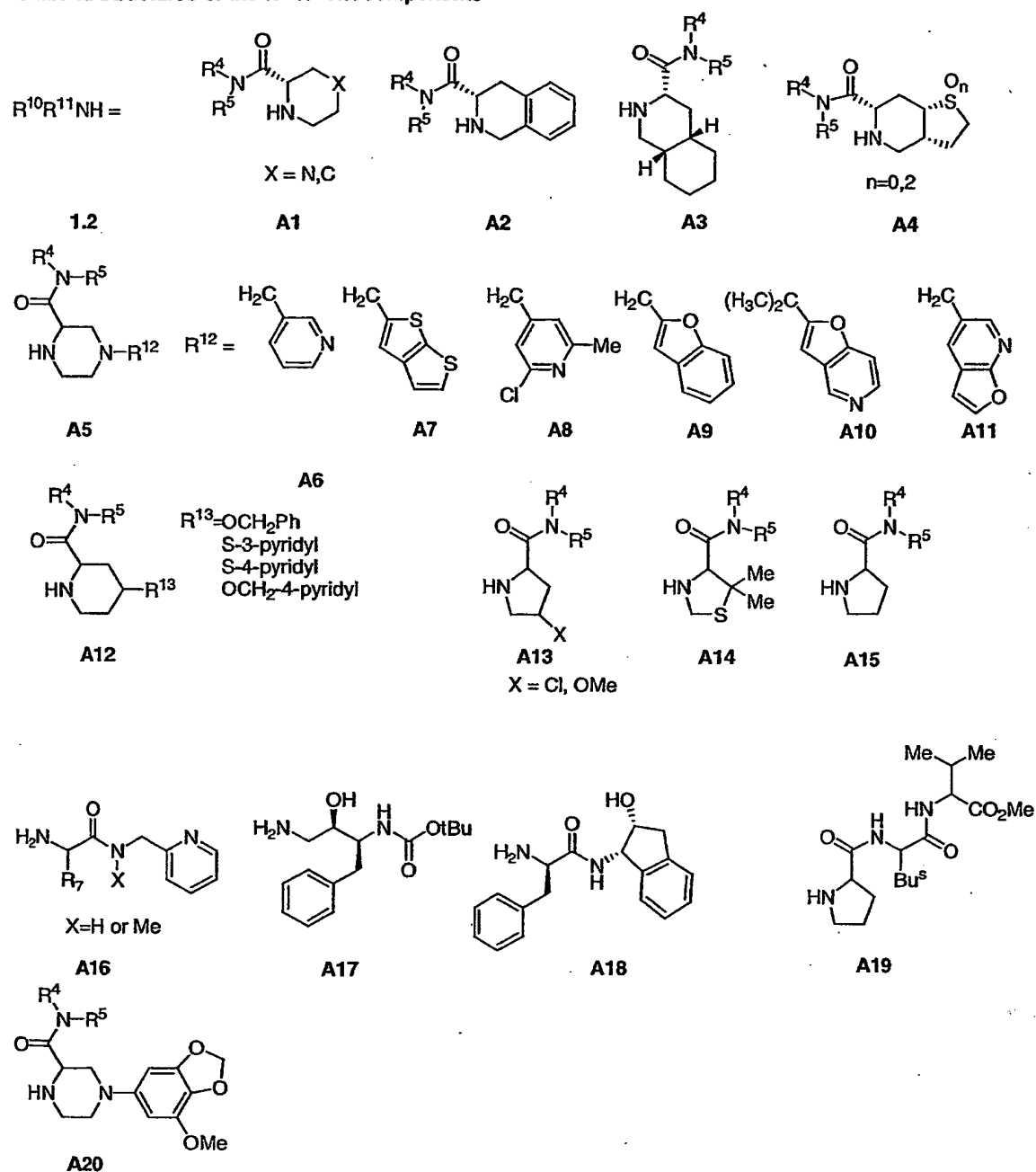
$R^{10}R^{11}NH =$

1.2

A1   X = N,C

A2

A3

A4   n=0,2

A5

$R^{12} =$

A6

A7

A8

A9

A10

A11

A12 R^{13}=OCH$_2$Ph
S-3-pyridyl
S-4-pyridyl
OCH$_2$-4-pyridyl

A13   X = Cl, OMe

A14

A15

A16   X=H or Me

A17

A18

A19

A20

R^7 = alkyl, CH$_2$SO$_2$CH$_3$, C(CH$_3$)$_2$SO$_2$CH$_3$, CH$_2$CONH$_2$, CH$_2$SCH$_3$, imidaz-4-ylmethyl, CH$_2$NHAc, CH$_2$NHCOCF$_3$

Chart 5 Structures of the R⁶XCH₂ groups.

$R^6SCH_2 =$

13

Y = H, F

14

$R^6CH_2 =$
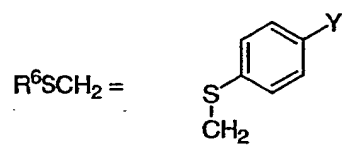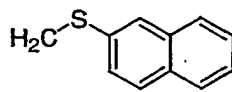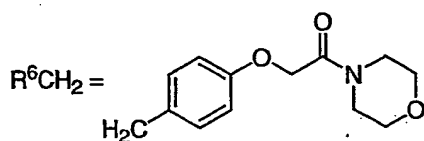
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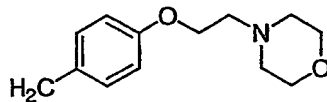
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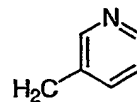
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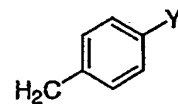
18

Y = H, OC₂H₅, OCH₂C₆H₅

Chart 6 Examples of the linking groups between the scaffold and the phosphonate moiety.

link   examples

direct bond

L1   L2   L3

L4   L5   L6

single carbon

L7   L8   L9

L10   L11   L12

multiple carbon

L13   L14   L15

hetero atoms

L16   L17   L18

L19   L20   L21
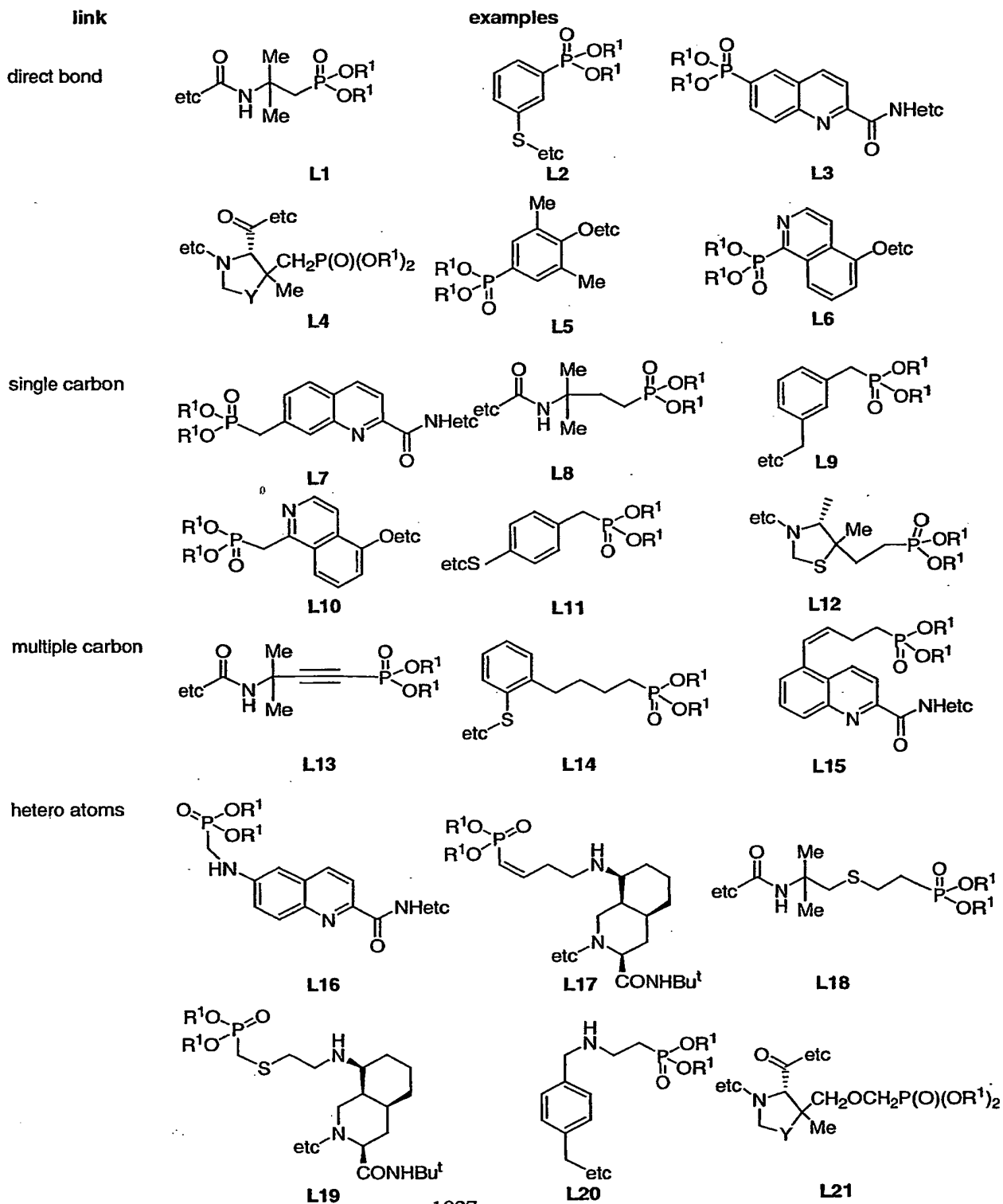
Chart 7 Examples of the linking groups between the scaffold and the phosphonate moiety.

link   examples

aryl, heteroaryl

L22   L23   L24

cycloalkyl

L25   L26

cyclized

L27   L28

amide

L29   L30   L31
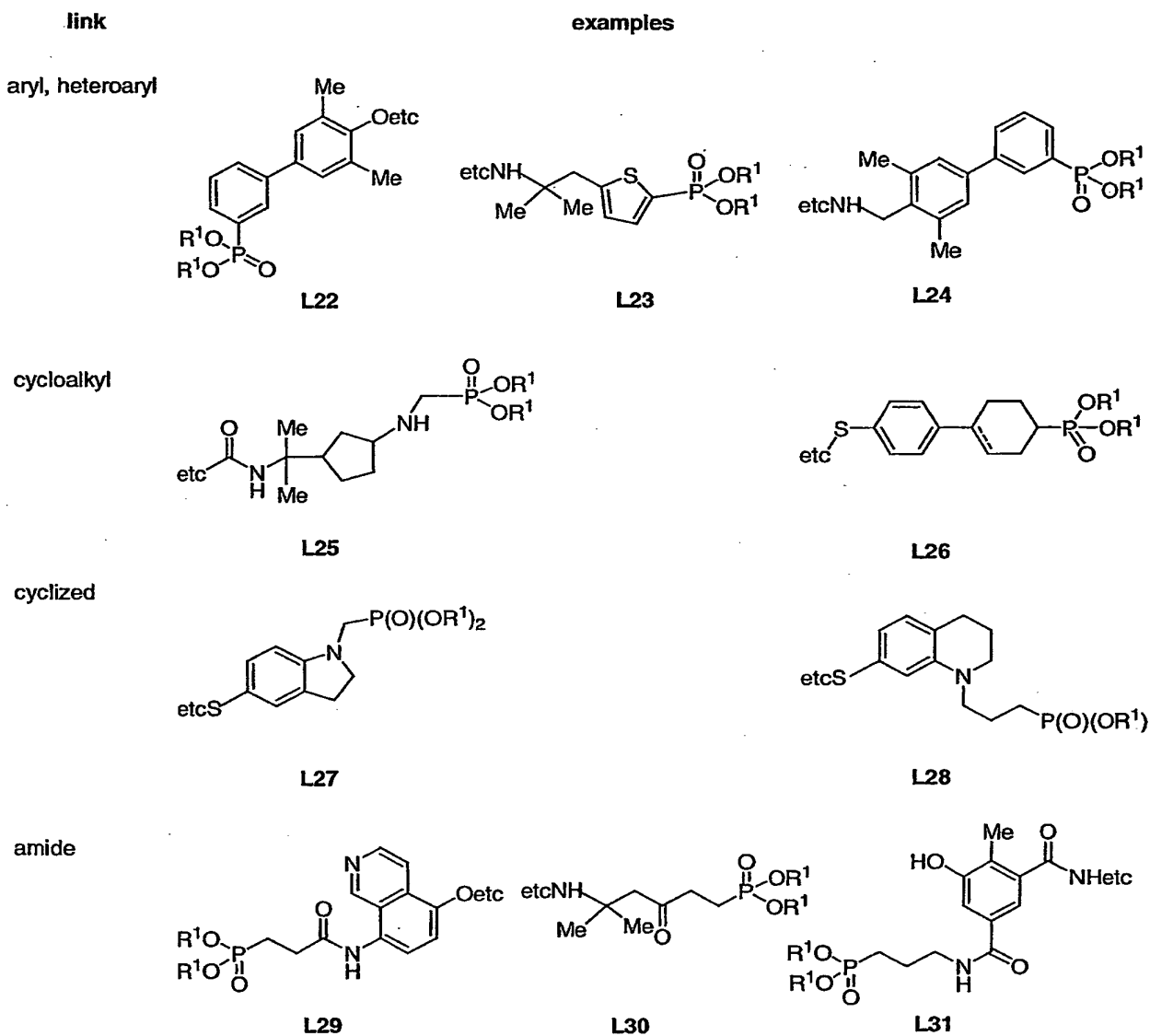
Protection of reactive substituents.

5

Depending on the reaction conditions employed, it may be necessary to protect certain
reactive substituents from unwanted reactions by protection before the sequence described,
and to deprotect the substituents afterwards, according to the knowledge of one skilled in the

art. Protection and deprotection of functional groups are described, for example, in Protective
Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.
Reactive substituents which may be protected are shown in the accompanying schemes as, for
example, [OH], [SH], etc.

5

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes 1 and 2 illustrate the preparation of the phosphonate esters **1** in which X is a direct
bond. As shown in Scheme **1**, a BOC-protected cyclic aminoacid **1.1** is reacted with an amine

10   **1.2** to afford the amide **1.3**. The carboxylic acid **1.1** in which Y is CH_2 and R^2 and R^3 are H is
commercially available (Bachem). The preparation of the carboxylic acid **1.1** in which Y is S
and R^2 and R^3 are CH_3 is described in Tet. Asym., 13, 2002, 1201; the preparation of the
carboxylic acid **1.1** in which Y is S and R^2 is H and R^3 is CH_3 is described in JP 60190795; the
preparation of the carboxylic acid **1.1** in which Y is S and R^2 and R^3 are H is described in EP

15   0574135; the preparation of the carboxylic acid **1.1** in which Y is CH_2, R^2 is H and R^3 is Cl is
described in EP 587311.

The preparation of amides from carboxylic acids and derivatives is described, for example, in
Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968,
p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff.

20   The carboxylic acid is reacted with the amine in the presence of an activating agent, such as,
for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence
of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-
protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.
Alternatively, the carboxylic acid may first be converted into an activated derivative such as

25   the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with
the amine, in the presence of an organic base such as, for example, pyridine, to afford the
amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by
treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl

30   chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a
catalytic amount of dimethylformamide. Preferably, equimolar amounts of the carboxylic acid
1.1 and the amine **1.2** are reacted together in tetrahydrofuran solution in the presence of

dicyclohexylcarbodiimide and N-hydroxysuccinimide, for example as described in EP 574135,
to yield the amide product 1.3. The BOC protecting group is then removed to give the free
amine 1.4. The removal of BOC protecting groups is described, for example, in Protective
Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

5   p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous
acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl
iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of
the compound 1.3 with 8M methanesulfonic acid in acetonitrile, as described in Tet. Asym.,
13, 2000, 1201, to afford the amine 1.4. The latter compound is then reacted with a carboxylic

10   acid 1.5, to afford the amide 1.6. The preparation of the carboxylic acid reactants 1.5 is
described below, (Schemes 41, 42). The reaction is performed under similar conditions to
those described above for the preparation of the amide 1.3. Preferably, equimolar amounts of
the amine 1.4 and the carboxylic acid 1.6 are reacted in tetrahydrofuran solution at ambient
temperature in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, for example

15   as described in EP 574135, to yield the amide 1.6. The BOC protecting group is then removed
from the product 1.6 to afford the amine 1.7, using similar conditions to those described above
for the removal of BOC protecting group from the compound 1.3. Preferably, the BOC group
is removed by treatment of the substrate 1.6 with a 4M solution of hydrogen chloride in
dioxan at 0°, for example as described in EP 574135, to give the amine product 1.7.

20   The amine is then reacted with a carboxylic acid 1.8, or an activated derivative thereof, in
which the substituent A is the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as
[OH], [SH], NH$_2$, Br, etc, as described herein, to afford the amide 1.9. The preparation of the
carboxylic acids 1.8 is described below in Schemes 45 - 49. The reaction between the amine
1.7 and the carboxylic acid 1.8 is conducted under similar conditions to those described above

25   for the preparation of the amides 1.3 and 1.6.

The procedures illustrated in Scheme 1 describe the preparation of the compounds 1.9 in
which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto,
such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

30   Scheme 2 depicts the conversion of the compounds 1.9 in which the A is a precursor to the
substituent link-$P(O)(OR^1)_2$ into the compounds 1. Procedures for the conversion of the

substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR^1)₂ are described

below in Schemes 45 - **101**.

In the preceding and following schemes, the conversion of various substituents into the group

link-P(O)(OR^1)₂ can be effected at any convenient stage of the synthetic sequence, as well as

5   at the end. The selection of an appropriate step for the introduction of the phosphonate

substituent is made after consideration of the chemical procedures required, and the stability of

the substrates to those procedures.

The phosphonate esters **5 - 12** in which the substituent R^{8}CO is derived from one of the

10   carboxylic acids **C38 - C49**, as shown in Chart **3c**, incorporate a carbamate linkage. Various

methods for the preparation of carbamate groups are described below in Scheme **102**.

In the above and succeeding examples, the nature of the phosphonate ester group can be

varied, either before or after incorporation into the scaffold, by means of chemical

transformations. The transformations, and the methods by which they are accomplished, are

15   described below (Scheme **103**)

Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes **3** and **4** illustrate the preparation of the phosphonate ester intermediates **1** in which X

20   is sulfur. Scheme **3** illustrates the reaction of the amine **1.3**, prepared as described in Scheme

1, with a carboxylic acid reagent **3.1**, to give the amide product **3.2**. The preparation of the

carboxylic acid reagents **3.1** is described below in Schemes **43** and **44**. The reaction between

the carboxylic acid **3.1** and the amine **1.3** is performed under similar conditions to those

described above for the preparation of the amide **1.6**. The amide product **3.2** is then subjected

25   to a deprotection reaction to remove the BOC substituent and afford the amine **3.3**. The

reaction is performed under similar conditions to those described in Scheme **1** for the removal

of BOC protecting groups. The amine product **3.3** is then reacted with a carboxylic acid **1.8**,

or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)₂, or

a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the

30   amide product **3.4**. The amide forming reaction is performed under similar conditions to those

described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme **3** describe the preparation of the compounds **3.4** in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme **4** depicts the conversion of the compounds **3.4** in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds **1**. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes **45** - **101**.

Scheme 1

1.1   **1.2**   **1.3**   **1.4**   **1.5**

1.6   **1.7**   **1.8**   **1.9**

Scheme 2

1.9   **1**

Scheme 3

1.3   **3.1**   **3.2**   **3.3**

1.8   **3.4**

Scheme 4

3.4   **1**
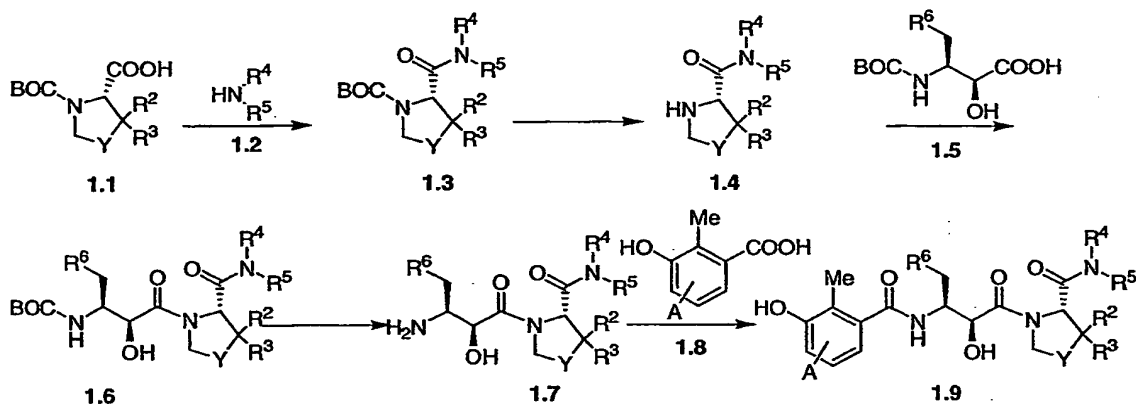
Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

Schemes 5 and 6 depict the preparation of the intermediate phosphonate esters 2 in which X is
direct bond. As shown in Scheme 5, the amine 1.7, prepared as described in Scheme 1, is
reacted with a carboxylic acid 5.1, or an activated derivative thereof, in which the substituent
A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH$_2$, Br,

5   etc, as described herein, to afford the amide product 5.2. The preparation of the carboxylic
acids 5.1 is described below in Schemes 50 - 56. The amide forming reaction is performed
under similar conditions to those described above for the preparation of the amide 1.9.

The procedures illustrated in Scheme 5 describe the preparation of the compounds 5.2 in

10   which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto,
such as [OH], [SH], [NH$_2$], Br, etc, as described herein.
Scheme 6 depicts the conversion of the compounds 5.2 in which the A is a precursor to the
substituent link-P(O)(OR^1)$_2$ into the compounds 2. Procedures for the conversion of the
substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described

15   below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 2 in which X is sulfur.

Schemes 7 and 8 depict the preparation of the intermediate phosphonate esters 2 in which X is

20   sulfur. As shown in Scheme 7, the amine 3.3, prepared as described in Scheme 3, is reacted
with a carboxylic acid 5.1, or an activated derivative thereof, in which the substituent A is the
group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH$_2$, Br, etc, as
described herein, to afford the amide product 7.1. The preparation of the carboxylic acids 5.1
is described below in Schemes 50 - 56. The amide forming reaction is performed under similar

25   conditions to those described above for the preparation of the amide 1.9.

The procedures illustrated in Scheme 7 describe the preparation of the compounds 7.1 in
which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto,
such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

30   Scheme 8 depicts the conversion of the compounds 7.1 in which the A is a precursor to the
substituent link-P(O)(OR^1)$_2$ into the compounds 2. Procedures for the conversion of the

substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described

below in Schemes 45 - 101.

Scheme 5

1.7   5.1   5.2

Scheme 6

5.2   2

Scheme 7

3.3   5.1   7.1

Scheme 8

7.1   2
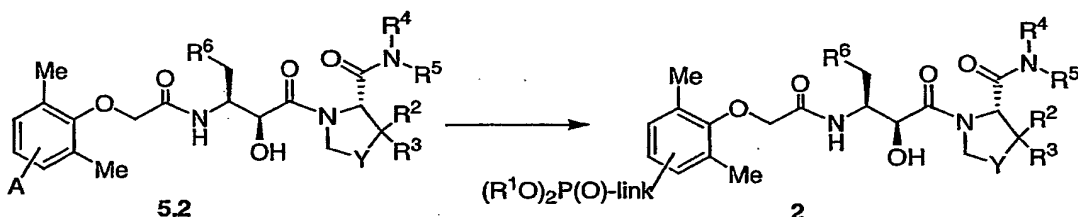
5   **Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.**

Schemes **9** and **10** depict the preparation of the intermediate phosphonate esters **3** in which X

is direct bond. As shown in Scheme **9**, the amine **1.7**, prepared as described in Scheme **1**, is

reacted with a carboxylic acid **9.1**, or an activated derivative thereof, in which the substituent

10   A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH$_2$, Br,

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etc, as described herein, to afford the amide product **9.2**. The preparation of the carboxylic acids **9.1** is described below in Schemes **57 - 60**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

5   The procedures illustrated in Scheme **9** describe the preparation of the compounds **9.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.
Scheme **10** depicts the conversion of the compounds **9.2** in which the group A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds **3**. Procedures for the conversion of the
10   substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes **45 - 101**.

Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

15   Schemes **11** and **12** depict the preparation of the intermediate phosphonate esters **3** in which X is sulfur. As shown in Scheme **11**, the amine **3.3**, prepared as described in Scheme **3**, is reacted with a carboxylic acid **9.1**, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH$_2$, Br, etc, as described herein, to afford the amide product **11.1**. The preparation of the carboxylic acids **9.1**
20   is described below in Schemes **57 - 60**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.
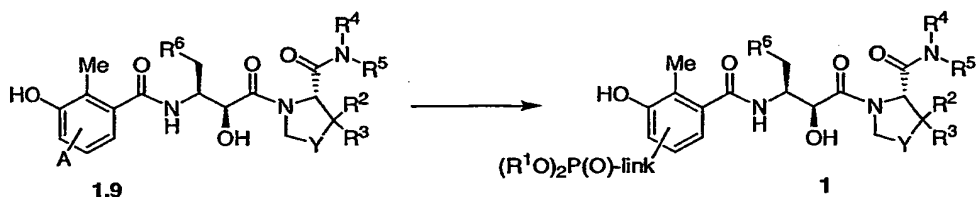The procedures illustrated in Scheme **11** describe the preparation of the compounds **11.1** in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

25

Scheme **12** depicts the conversion of the compounds **11.1** in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds **3**. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes **45 - 101**.
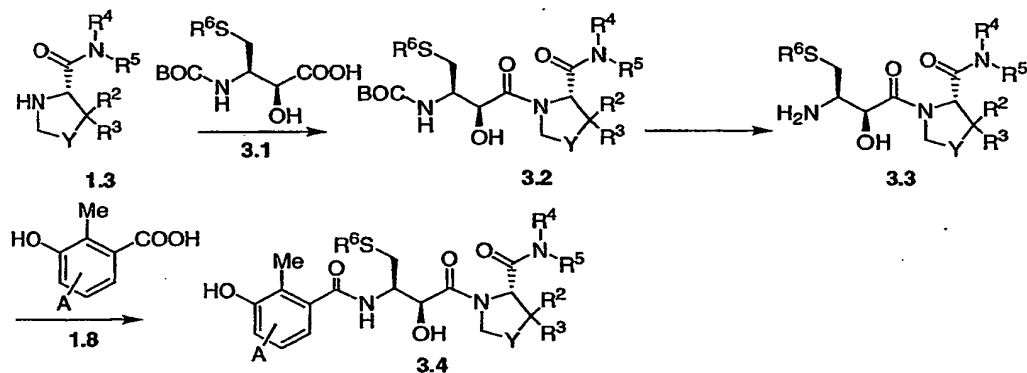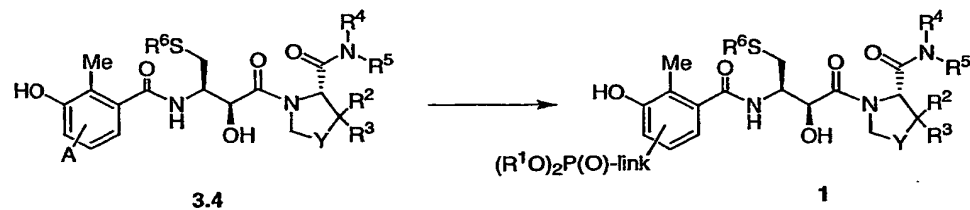
30

Scheme 9

Scheme 10

Scheme 11

Scheme 12

Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

Schemes **13** and **14** depict the preparation of the intermediate phosphonate esters **4** in which X is direct bond. As shown in Scheme **13**, the amine **1.7**, prepared as described in Scheme **1**, is reacted with a carboxylic acid **13.1**, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH$_2$, Br, etc, as described herein, to afford the amide product **13.2**. The preparation of the carboxylic acids **13.1** is described below in Schemes **61** - **66**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme 13 describe the preparation of the compounds 13.2 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 14 depicts the conversion of the compounds 13.2 in which the A is a precursor to the

5   substituent link-P(O)(OR^1)$_2$ into the compounds 4. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.
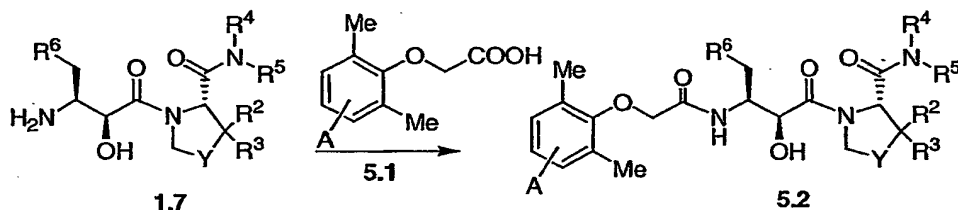
10

Schemes 15 and 16 depict the preparation of the intermediate phosphonate esters 4 in which X is sulfur. As shown in Scheme 15, the amine 3.3, prepared as described in Scheme 3, is reacted with a carboxylic acid 13.1, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH$_2$, Br, etc, as

15   described herein, to afford the amide product 15.1. The preparation of the carboxylic acids 13.1 is described below in Schemes 61 - 66. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

The procedures illustrated in Scheme 15 describe the preparation of the compounds 15.1 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto,

20   such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 16 depicts the conversion of the compounds 15.1 in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds 4. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.
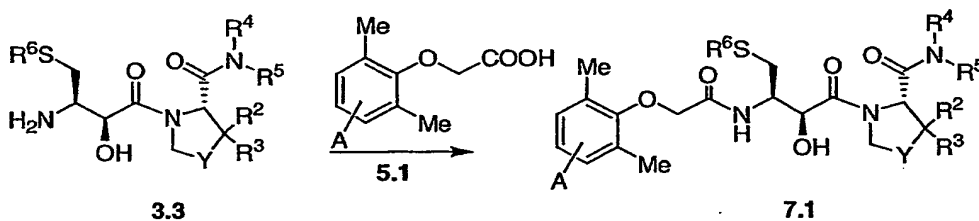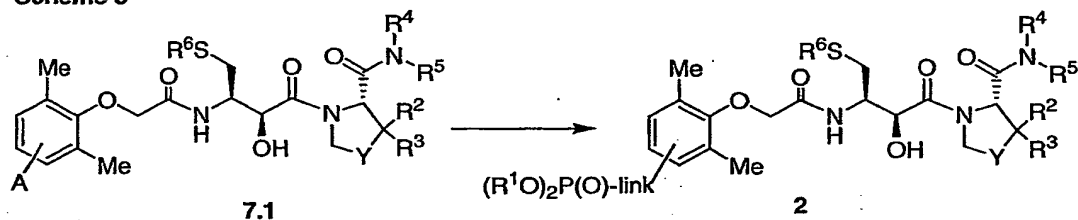
25

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes 17 and 18 show the preparation of the intermediate phosphonate esters 5 in which X is a direct bond. As depicted in Scheme 17, the amine 1.4, prepared as described in Scheme 1,

30   is reacted with the carboxylic acid 17.1, or an activated derivative thereof, to yield the amide product 17.2. The preparation of the carboxylic acids 17.1 in which the group A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, is

described in Schemes **67 – 71**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. The BOC protecting group is then removed from the product **17.2** to afford the amine **17.3**. The deprotection reaction is performed using similar conditions to those described above in Scheme **1**. The

5   resultant amine **17.3** is then reacted with a carboxylic acid R^8COOH or activated derivative thereof, **17.4** to give the amide **17.5**. For those carboxylic acids R^8COOH listed in Charts **3a** and **3b**, the reaction is performed using similar conditions to those described above for the preparation of the amide **1.9**, (Scheme 1); for those carboxylic acids R^8COOH listed in Chart **3c**, the reaction is performed using conditions described below (Scheme **102**) for the

10   preparation of carbamates.

The procedures illustrated in Scheme **17** describe the preparation of the compounds **17.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

15   Scheme **18** depicts the conversion of the compounds **17.5** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45 - 101**.

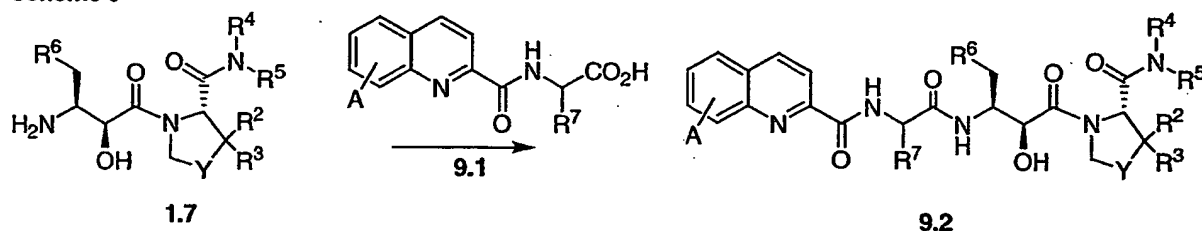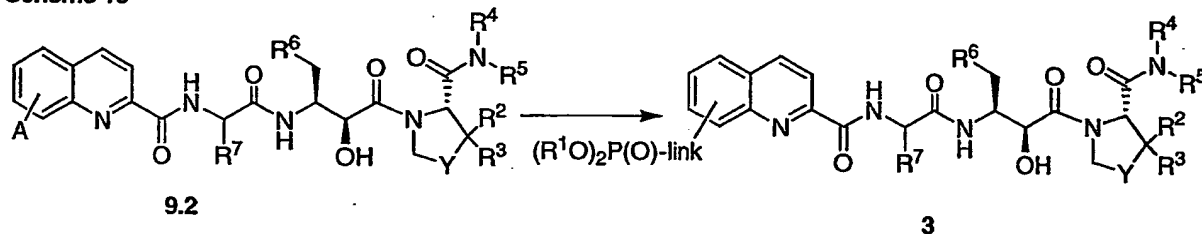20   **Preparation of the phosphonate ester intermediates 5 in which X is sulfur.**

Schemes **19** and **20** show the preparation of the intermediate phosphonate esters **5** in which X is sulfur. As depicted in Scheme **19**, the amine **1.4**, prepared as described in Scheme **1**, is reacted with the carboxylic acid **19.1**, or an activated derivative thereof, to yield the amide

25   product **19.2**. The preparation of the carboxylic acids **19.1** in which the group A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, is described in Schemes **72 - 83**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. The BOC protecting group is then removed from the product **19.2** to afford the amine **19.3**. The deprotection

30   reaction is performed using similar conditions to those described above in Scheme **1**. The resultant amine **19.3** is then reacted with a carboxylic acid R^8COOH or activated derivative thereof, **19.4** to give the amide **19.4**. For those carboxylic acids R^8COOH listed in Charts **3a**

and **3b**, the reaction is performed using similar conditions to those described above for the preparation of the amide **1.9**, (Scheme **1**); for those carboxylic acids R^8COOH listed in Chart **3c**, the reaction is performed using conditions described below (Scheme **102**) for the preparation of carbamates.

5

The procedures illustrated in Scheme **19** describe the preparation of the compounds **19.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme **20** depicts the conversion of the compounds **19.4** in which the A is a precursor to the

10 substituent link-$P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45 - 101**.
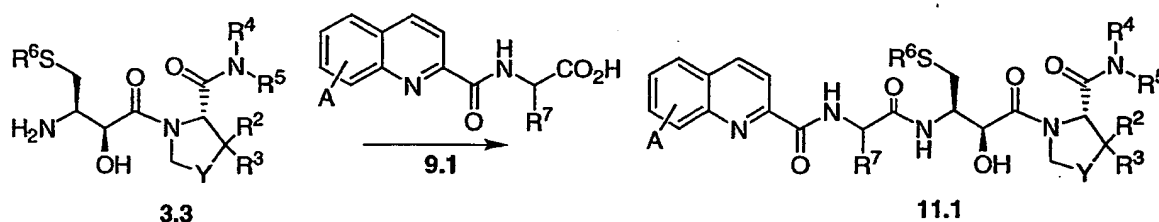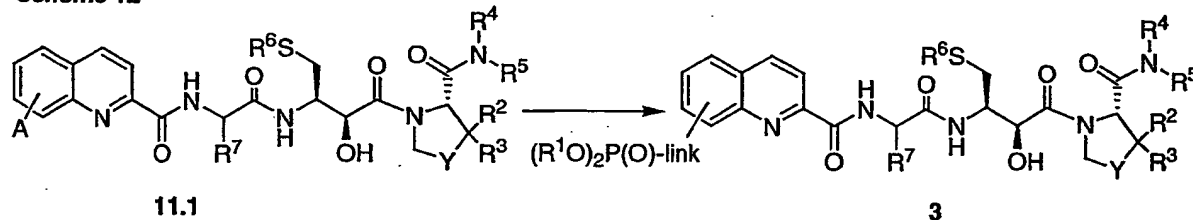
Scheme 13

1.7   **13.1**   **13.2**

Scheme 14

13.2 $(R^1O)_2P(O)$-link   **4**

Scheme 15

3.3   **13.1**   **15.1**

Scheme 16

15.1 $(R^1O)_2P(O)$-link   **4**

Scheme 17

Scheme 18

Scheme 19
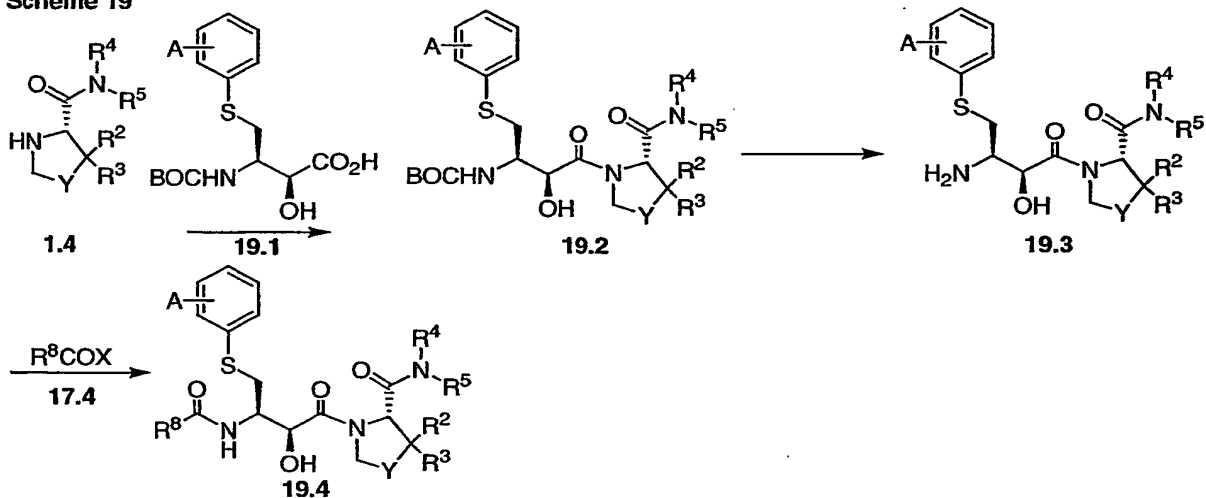
Scheme 20

Preparation of the phosphonate ester intermediates 6 in which X is a direct bond.

Schemes 21 and 22 illustrate the preparation of the phosphonate esters 6 in which X is a direct

5   bond. In this procedure, the carboxylic acid 21.1, in which the group A is the substituent link-
P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described
herein, is reacted with the amine 1.2 to afford the amide 21.2. The preparation of the
carboxylic acids 21.1 is described below in Schemes 98 - 101. The reaction is performed under
similar conditions to those described in Scheme 1 for the preparation of the amide 1.3. The

10   product 21.2 is then deprotected to yield the free amine 21.3, using the procedures described
above for the removal of BOC groups. The amine 21.3 is then converted, by reaction with the
carboxylic acid 1.5, into the amide 21.4, using the conditions described above for the
preparation of the amide 1.6. The amide 21.4 is then deprotected to afford the amine 21.5, and
the latter compound is acylated with the carboxylic acid 17.4 to give the amide 21.6.

15

The procedures illustrated in Scheme 21 describe the preparation of the compounds 21.6 in
which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto,
such as [OH], [SH], [NH₂], Br, etc, as described herein.
Scheme 22 depicts the conversion of the compounds 21.6 in which the A is a precursor to the

20   substituent link-P(O)(OR¹)₂ into the compounds 6. Procedures for the conversion of the
substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described
below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 6 in which X is sulfur.

25

Schemes 23 and 24 illustrate the preparation of the phosphonate esters 6 in which X is sulfur.
In the procedure shown in Scheme 23, the amine 21.3, prepared as described in Scheme 21, is
reacted with the carboxylic acid 3.1 to afford the amide 23.1. The reaction is performed under
similar conditions to those described in Scheme 1 for the preparation of the amide 1.3. The

30   product 23.1 is then converted, by means of deprotection and acylation, as shown in Scheme
21 for the conversion of the compound 21.4 into the compound 21.6, into the amide product
23.2.

The procedures illustrated in Scheme 23 describe the preparation of the compounds 23.2 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

5   Scheme 24 depicts the conversion of the compounds 23.2 in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds 6. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.

10   **Preparation of the phosphonate ester intermediates 7 in which X is a direct bond.**

Schemes 25 and 26 illustrate the preparation of the phosphonate esters 7 in which X is a direct bond. As shown in Scheme 25, the carboxylic acid 1.1 is reacted with the amine 25.1, in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as
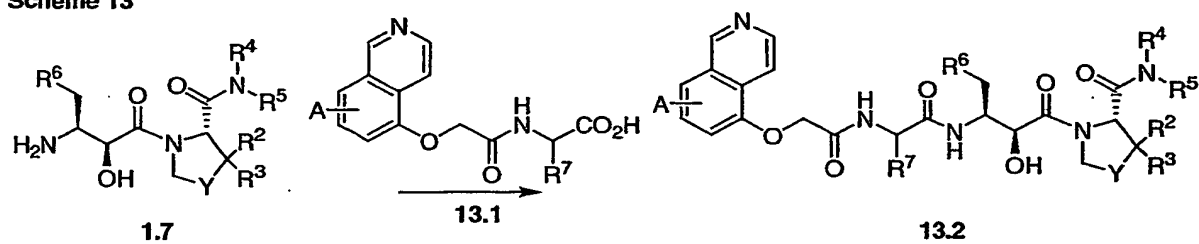
15   [OH], [SH], [NH$_2$], Br, etc, as described herein, to produce the amide 25.2. The reaction is performed using similar conditions to those described above for the preparation of the amide 1.3. The preparation of the amines 25.1 is described below, in Schemes 84 - 87. The amide product 25.2 is then transformed, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.2 into the compound 21.6, into the compound 25.3.

20

The procedures illustrated in Scheme 25 describe the preparation of the compounds 25.3 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 25 depicts the conversion of the compounds 25.3 in which the A is a precursor to the

25   substituent link-P(O)(OR^1)$_2$ into the compounds 7. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 7 in which X is sulfur.

30

Schemes 27 and 28 illustrate the preparation of the phosphonate esters 7 in which X is sulfur. As shown in Scheme 27, the BOC-protected amine 25.2 is deprotected to yield the free amine

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27.1, using the conditions previously described. The amine 27.1 is then reacted, as described above, with the carboxylic acid 3.1 to afford the amide 27.2. The latter compound is then transformed, as described above, (Scheme 23) into the product 27.3.

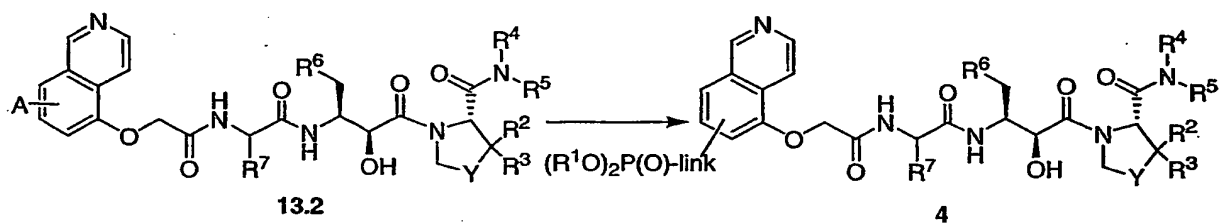5   The procedures illustrated in Scheme 27 describe the preparation of the compounds 27.3 in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.
Scheme 28 depicts the conversion of the compounds 27.3 in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds 7. Procedures for the conversion of the

10   substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes 45 - 101.
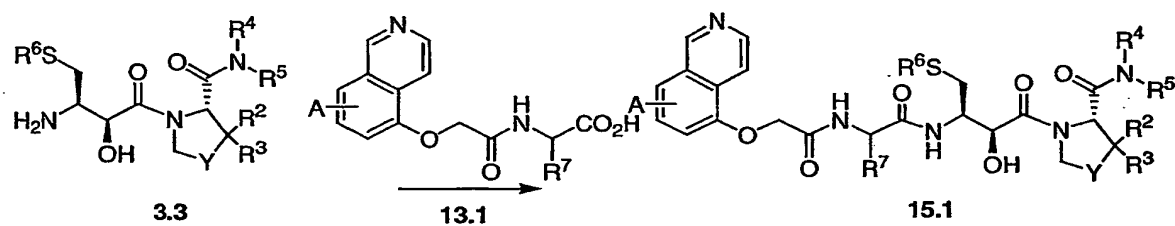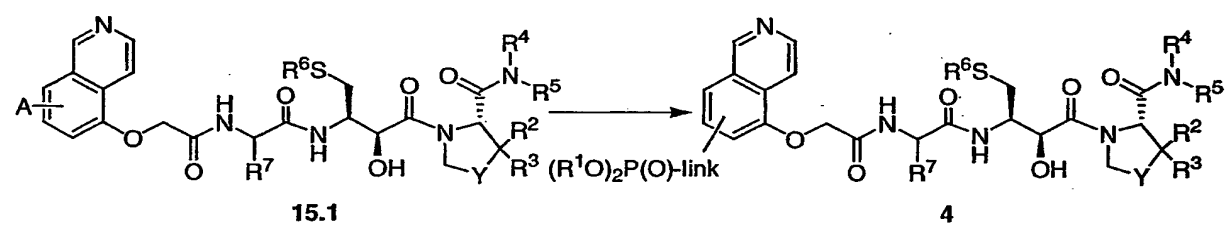
Scheme 21
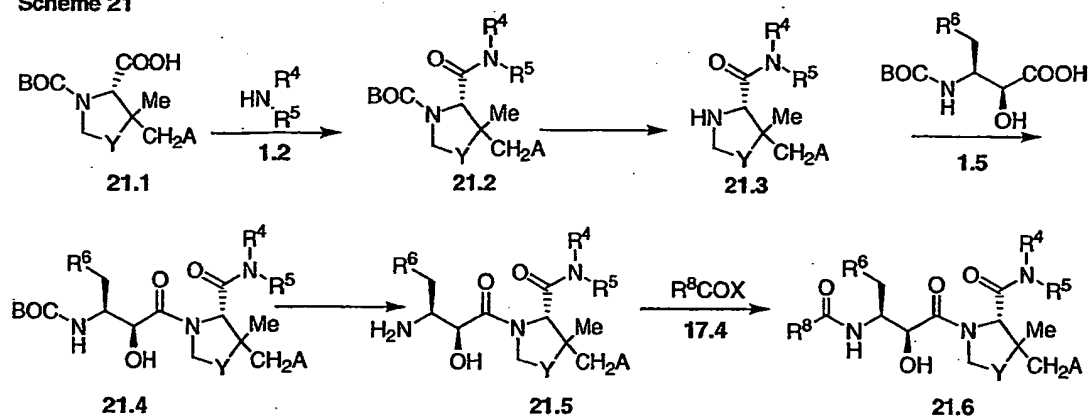
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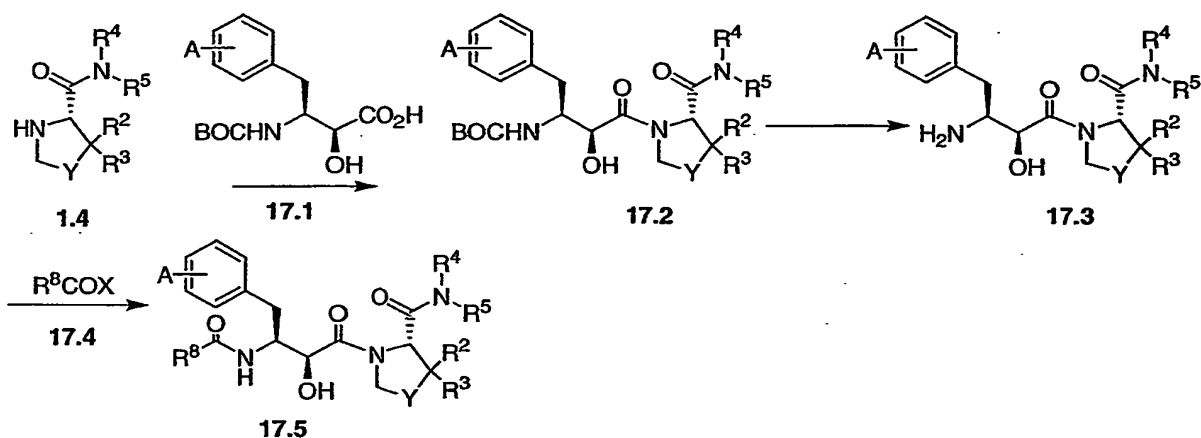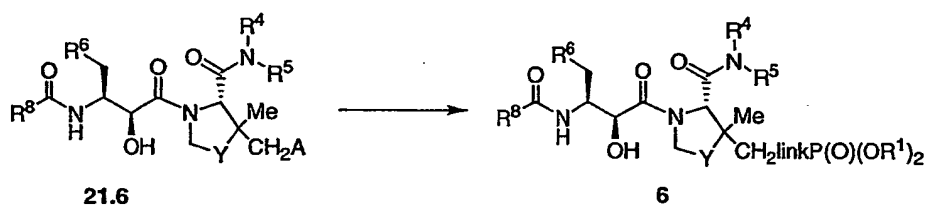

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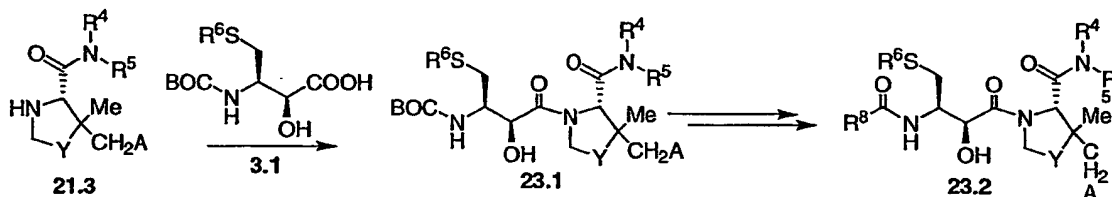
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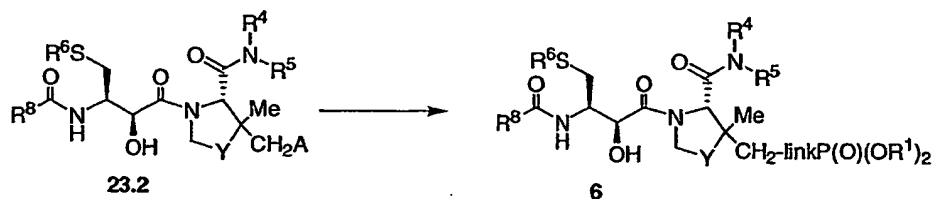
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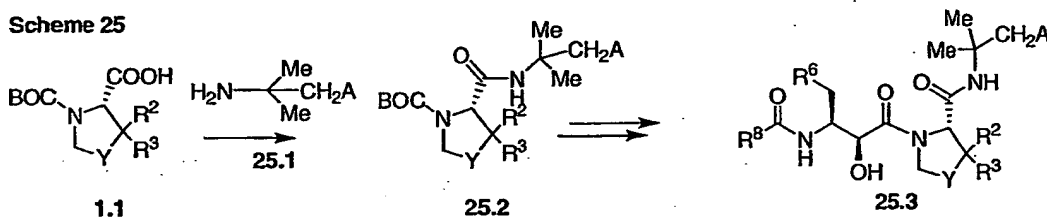
1.1   25.2   25.3

Scheme 26

25.3   7

Scheme 27

25.2   27.1   3.1   27.2
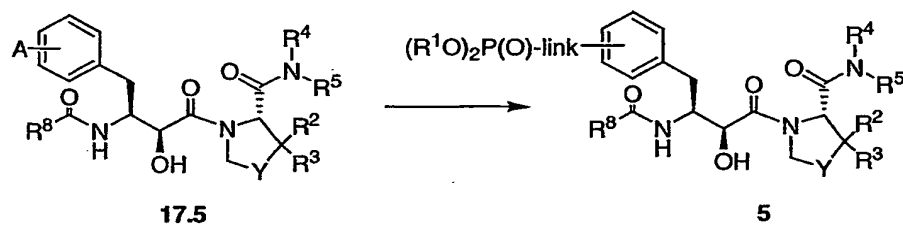

27.3

Scheme 28

27.3   7
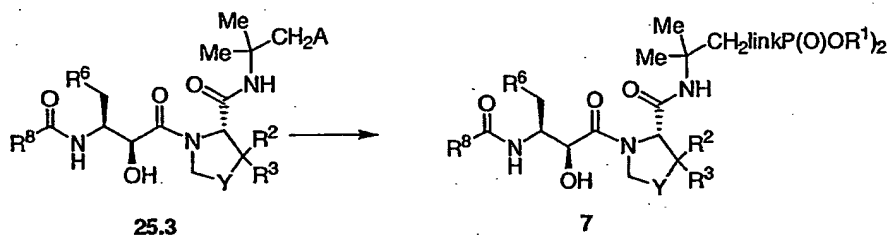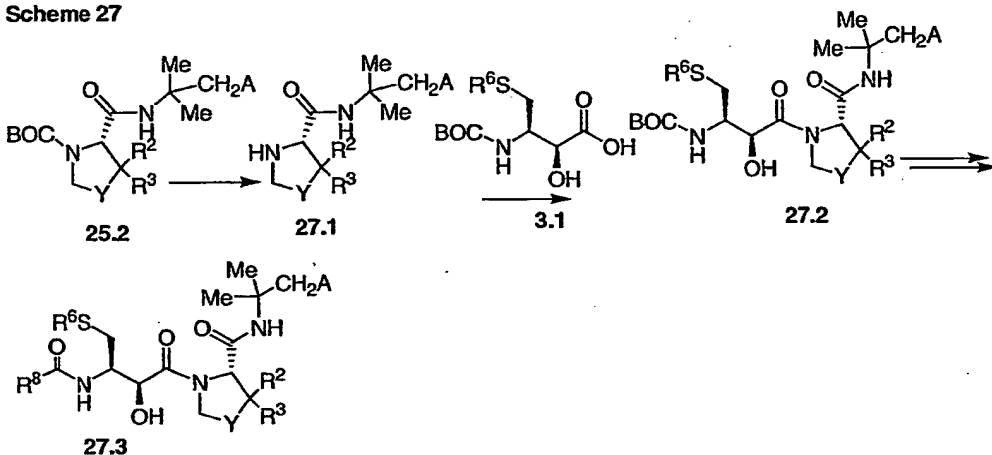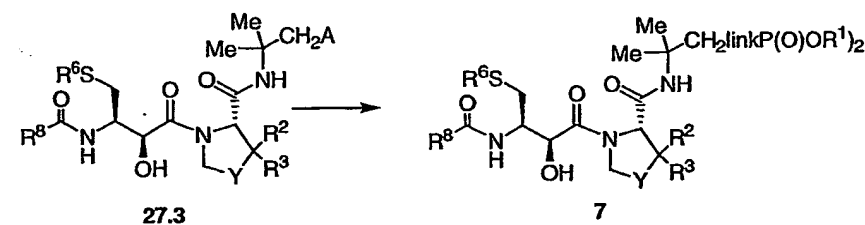
Preparation of the phosphonate ester intermediates 8 in which X is a direct bond.

Schemes 29 and 30 illustrate the preparation of the phosphonate esters 8 in which X is a direct

5   bond. As shown in Scheme 29, the carboxylic acid 1.1 is reacted with the amine 29.1, in which

the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as

[OH], [SH], [NH$_2$], Br, etc, as described herein, to produce the amide 29.2. The reaction is

performed using similar conditions to those described above for the preparation of the amide 1.3. The preparation of the amines 29.1 is described below, in Schemes 86 - 88. The amide product 29.2 is then transformed, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.2 into the compound 21.6, into the compound 29.3.

5

The procedures illustrated in Scheme 29 describe the preparation of the compounds 29.3 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 30 depicts the conversion of the compounds 29.3 in which the A is a precursor to the

10   substituent link-P(O)(OR^1)$_2$ into the compounds 8. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 8 in which X is sulfur.

15

Schemes 31 and 32 illustrate the preparation of the phosphonate esters 8 in which X is sulfur. As shown in Scheme 31, the BOC-protected amine 29.2 is deprotected to yield the free amine 31.1, using the conditions previously described. The amine 31.1 is then reacted, as described above, with the carboxylic acid 3.1 to afford the amide 31.2. The latter compound is then

20   transformed, as described above, (Scheme 23) into the product 31.3.

The procedures illustrated in Scheme 31 describe the preparation of the compounds 31.3 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

25   Scheme 32 depicts the conversion of the compounds 31.3 in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds 8. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.
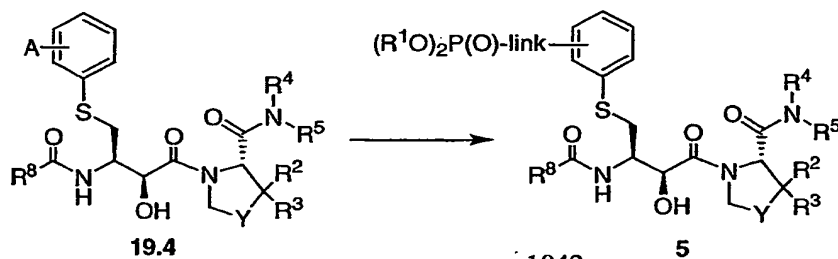
30   **Preparation of the phosphonate ester intermediates 9 in which X is a direct bond.**

Schemes 33 and 34 illustrate the preparation of the phosphonate esters 9 in which X is a direct bond. As shown in Scheme 33, the carboxylic acid 1.5 is reacted with the amine 33.1, in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein, to produce the amide 33.2. The reaction is
5   performed using similar conditions to those described above for the preparation of the amide 1.6 in Scheme 1. The preparation of the amines 33.1 is described below, in Schemes 91 - 97. The amide product 33.2 is then transformed into the compound 33.3, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.4 into the compound 21.6.

10   The procedures illustrated in Scheme 33 describe the preparation of the compounds 33.3 in which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 34 depicts the conversion of the compounds 33.3 in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds 9. Procedures for the conversion of the
15   substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 9 in which X is sulfur.

20   Schemes 35 and 36 illustrate the preparation of the phosphonate esters 9 in which X is sulfur. As shown in Scheme 35 the amine 33.2 is transformed into 35.1 by similar means described above (Scheme 23) for converting 21.3 into 23.2.

The procedures illustrated in Scheme 35 describe the preparation of the compounds 35.1 in
25   which the substituent A is either the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 36 depicts the conversion of the compounds 35.1 in which the A is a precursor to the substituent link-P(O)(OR^1)$_2$ into the compounds 9. Procedures for the conversion of the substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-P(O)(OR^1)$_2$ are described
30   below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 10 in which X is a direct bond.

Schemes 37 and 38 illustrate the preparation of the phosphonate esters 10 in which X is a

direct bond. As shown in Scheme 37, the carboxylic acid 1.5 is reacted with the amine 37.1, in

which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto,

5   such as [OH], [SH], [NH$_2$], Br, etc, as described herein, to produce the amide 37.2. The

reaction is performed using similar conditions to those described above for the preparation of

the amide 1.6. The preparation of the amines 37.1 is described below, in Scheme 91-97. The

amide product 37.2 is then transformed into the compound 37.3, using the sequence of

reactions shown in Scheme 21 for the conversion of the amide 21.4 into the compound 21.6.

10

The procedures illustrated in Scheme 37 describe the preparation of the compounds 37.3 in

which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto,

such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 38 depicts the conversion of the compounds 37.3 in which the A is a precursor to the

15   substituent link-$P(O)(OR^1)_2$ into the compounds 10. Procedures for the conversion of the

substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-$P(O)(OR^1)_2$ are described

below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 10 in which X is sulfur.

20

Schemes 39 and 40 illustrate the preparation of the phosphonate esters 10 in which X is sulfur.

As shown in Scheme 39 the amine 37.1 is transformed into the product 39.1, as described

above, (Scheme 23) for the conversion of 21.3 into 23.2.

25   The procedures illustrated in Scheme 39 describe the preparation of the compounds 39.1 in

which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto,

such as [OH], [SH], [NH$_2$], Br, etc, as described herein.

Scheme 40 depicts the conversion of the compounds 39.1 in which the A is a precursor to the

substituent link-$P(O)(OR^1)_2$ into the compounds 10. Procedures for the conversion of the

30   substituents [OH], [SH], [NH$_2$], Br etc into the substituent link-$P(O)(OR^1)_2$ are described

below in Schemes 45 - 101.

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Scheme 29

Scheme 30
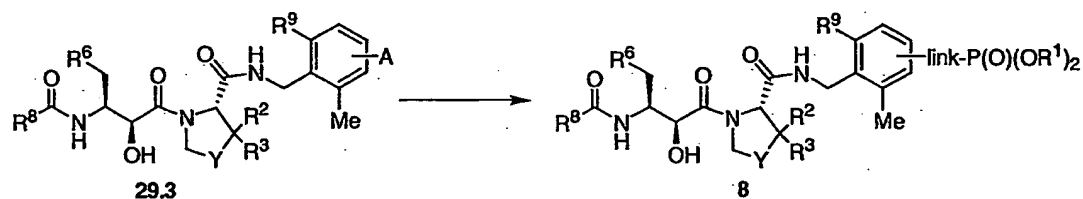
Scheme 31
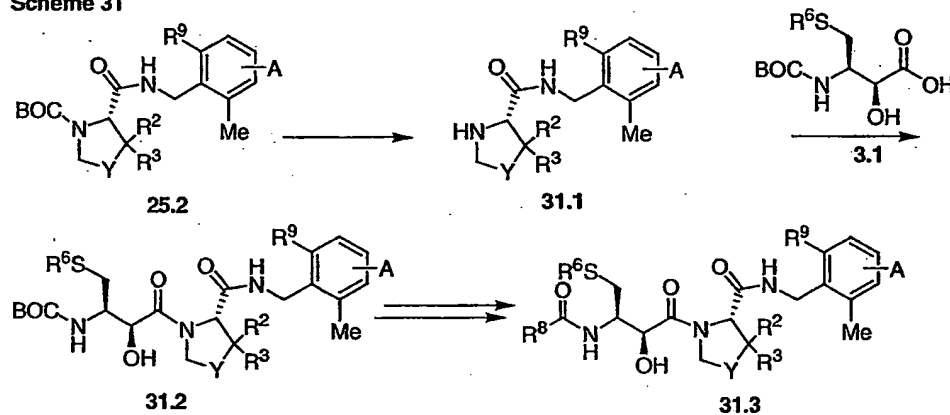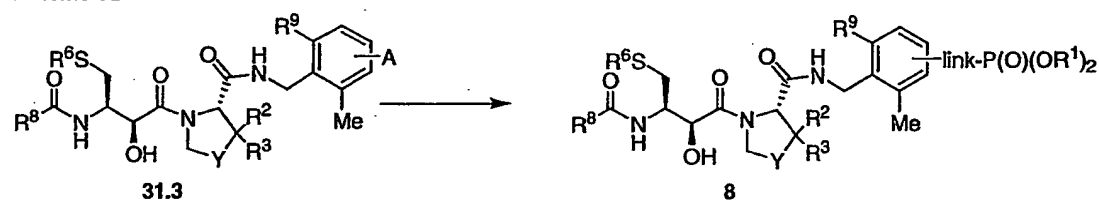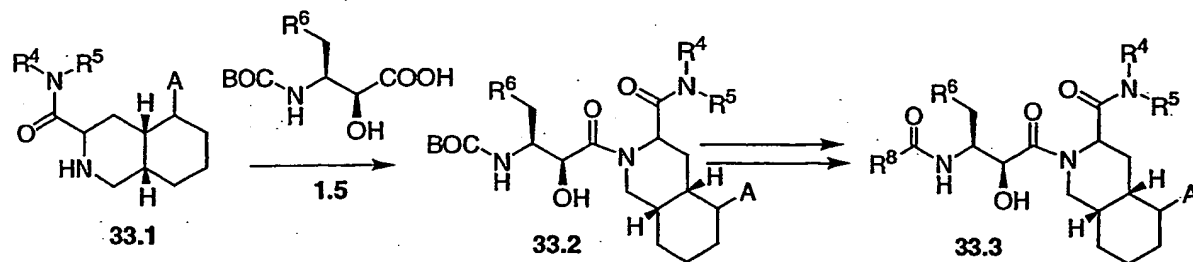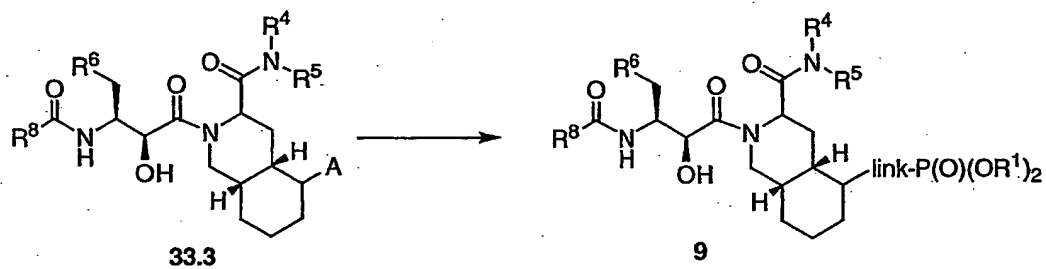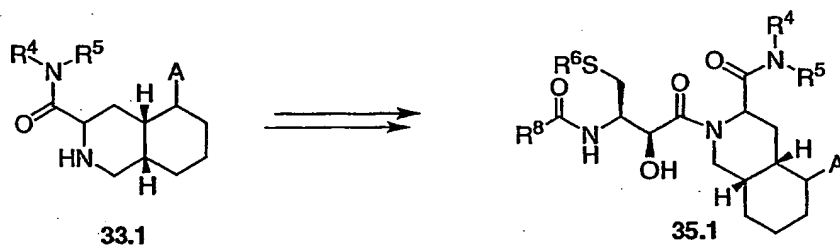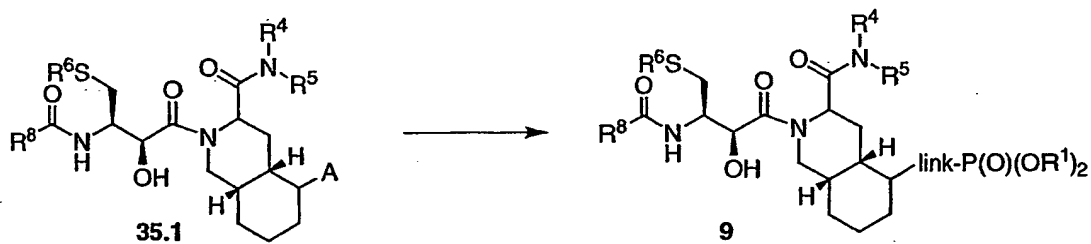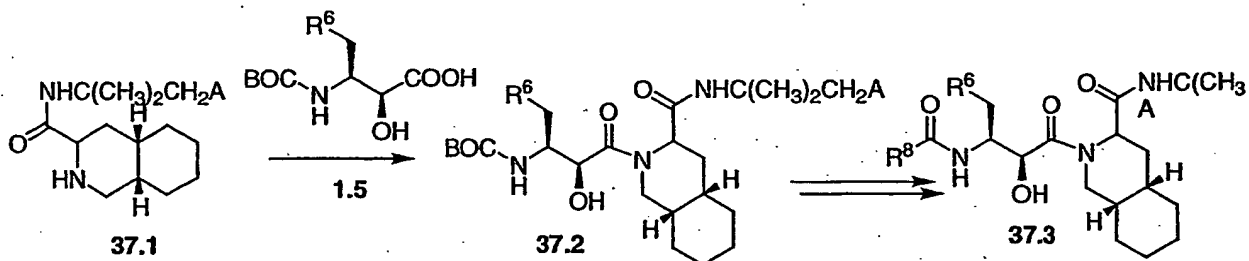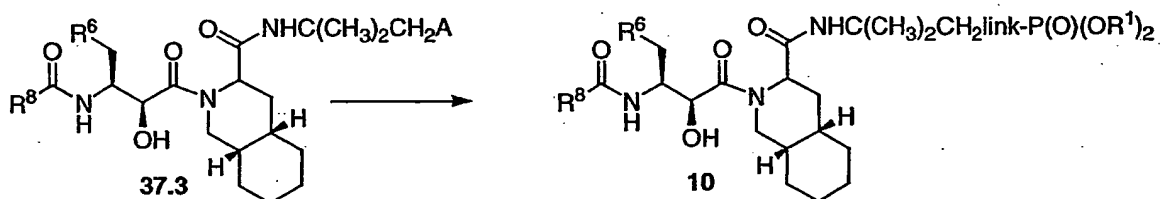
Scheme 32

Scheme 33

33.1   **1.5**   **33.2**   **33.3**

Scheme 34

33.3   **9**

Scheme 35

33.1   **35.1**

Scheme 36

35.1   **9**

Scheme 37

37.1   **1.5**   **37.2**   **37.3**

Scheme 38

37.3   **10**

Scheme 39

37.1   **39.1**

Scheme 40

39.1   **10**
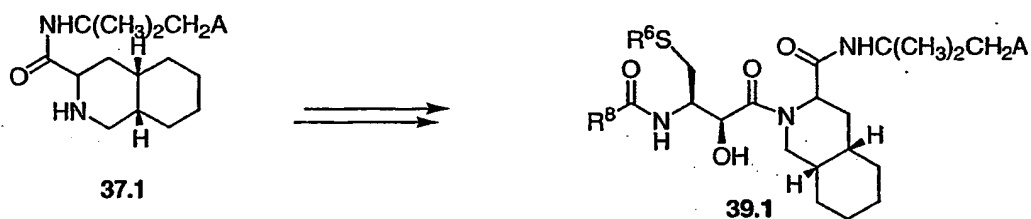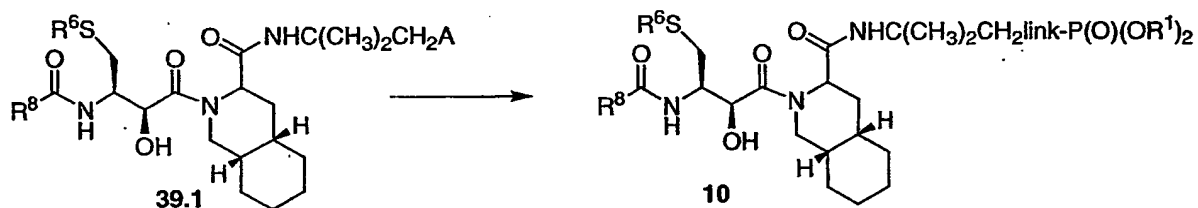
Preparation of the BOC-protected aminohydroxy phenylbutanoic acids 1.5.

5   The preparation of the butanoic acid derivatives **1.5** in which R^6 is phenyl is described, for
example, in Tet. Asym., 2002, 13, 1201, Eur. J. Med. Chem., 2000, 35, 887, Chem. Pharm.
Bull., 2000, 48, 1310, J. Med. Chem., 1994, 37, 2918, J. Chem. Res., 1999, 282 and J. Med.

Chem., 1993, 36, 211. The analogs **1.5** in which the substituent R^6 is as described in Chart **5** are prepared by analogous reaction sequences.

Schemes **41** and **42** illustrate two alternative procedures for the preparation of the reactants

5   **1.5**. As shown in Scheme **41**, the BOC-protected aminoacid **41.1** is converted into the corresponding aldehyde **41.3**. Numerous methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The conversion is effected by direct reduction of the carboxylic acid, for example employing

10   diisobutyl aluminum hydride, as described in J. Gen. Chem. USSR., 34, 1021, 1964, or alkyl borane reagents, for example as described in J. Org. Chem., 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in J. Med. Chem., 1994, 37, 2918, to afford the aldehyde **41.3**. Alternatively, the carboxylic acid is

15   reduced to the corresponding carbinol **41.2**. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in J. Am. Chem. Soc., 92, 1637, 1970, or by lithium aluminum hydride, as described in Org. Reac., 6, 649, 1951. The resultant carbinol **41.2** is then converted into the

20   aldehyde **41.3** by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in J.Org. Chem., 50, 262, 1985, or silver carbonate, as described in Compt. Rend. Ser. C., 267, 900, 1968, or dimethyl

25   sulfoxide/acetic anhydride, as described in J. Am. Chem. Soc., 87, 4214, 1965. Preferably, the carbinol **41.2** is converted into the aldehyde **41.3** by oxidation with pyridine-sulfur trioxide in dimethyl sulfoxide, as described in Eur. J. Med. Chem., 35, 2000, 887. The aldehyde **41.3** is then transformed into the cyanohydrin **1.4**. The transformation of an aldehyde into the corresponding cyanohydrin is effected by reaction with an alkali metal cyanide such as

30   potassium cyanide, in an aqueous organic solvent mixture. Preferably, a solution of the aldehyde in ethyl acetate is reacted with an aqueous solution of potassium cyanide, as described in Eur. J. Med. Chem., 35, 2000, 887, to yield the cyanohydrin **41.4**. Optionally, a

methanolic solution of the aldehyde is first treated with an aqueous solution of sodium

bisulfite, and the bisulfite adduct which is formed in situ is then reacted with an aqueous

solution of sodium cyanide, as described in J. Med. Chem., 37, 1994, 2918, to give the

cyanohydrin 41.4. The latter compound is then hydrolyzed to afford the hydroxyacid product

5   41.5. The hydrolysis is effected under acidic conditions; for example, the cyanohydrin 41.4 is

heated in a mixture of concentrated hydrochloric acid and dioxan, as described in Eur. J. Med.

Chem., 35, 2000, 887, optionally in the presence of anisole, as described in J. Med. Chem., 37,

1994, 2918, to afford the hydroxyacid product, from which the (2S), (3S) isomer 41.5 is

isolated. The BOC protecting group is then attached, for example by reaction of the aminoacid

10   41.5 with BOC anhydride in aqueous tetrahydrofuran containing triethylamine, as described in

Eur. J. Med. Chem., 35, 2000, 887.

Alternatively, the BOC-protected aminohydroxy phenylbutanoic acids 1.5 are obtained by

means of the reaction sequence shown in Scheme 42. In this sequence, the N, N-dibenzyl

15   aminoacid ester 42.1, prepared as described in Tet., 1995, 51, 6397, is converted, using the

procedures described above in Scheme 41, into the corresponding aldehyde 42.2. The latter

compound is then reacted with a silylmethyl Grignard reagent, for example

isopropoxydimethylsilylmethylmagnesium chloride 42.3, to give the carbinol product 42.4.

Preferably, the aldehyde and ca. two molar equivalents of the Grignard reagent are reacted in

20   tetrahydrofuran solution at 0°, as described in Tet. Asym., 2002, 13, 1201. The silyl carbinol

42.4 is then reacted with aqueous ammonium chloride, as described in Tet. Asym., 2002, 13,

1201, to give the diol 42.5. The N-benzyl groups are then removed to afford the free amine

42.6. The removal of N-benzyl groups is described, for example, in Protective Groups in

Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 365.

25   Benzyl groups are removed by catalytic hydrogenation in the presence of hydrogen or a

hydrogen donor, by reduction with sodium in ammonia, by treatment with trichloroethyl

chloroformate, or by oxidation, for example by the use of ruthenium tetroxide or 3-

chloroperoxybenzoic acid and ferrous chloride. Preferably, the debenzylation is effected by

hydrogenation of the substrate 42.5 in ethanol at ca 50° in the presence of 5% palladium on

30   carbon catalyst, as described in Tet. Asym., 2002, 13, 1201, to produce the amine 42.6. The

BOC protecting group is then attached using the procedures described above, and the

resultant product 42.7 is oxidized to give the carboxylic acid 1.5. The oxidation of carbinols to

afford the corresponding carboxylic acid is described in Comprehensive Organic

Transformations, by R. C. Larock, VCH, 1989, p. 835. The conversion can be effected by the

sue of oxidizing agents such as chromium trioxide in acetic acid, potassium permanganate,

ruthenium tetroxide or silver oxide. Preferably, the transformation is effected by the use of

5   sodium chlorite and sodium hypochlorite in aqueous acetonitrile in the presence of a pH 6.7

phosphate buffer and a catalytic amount of 2,2,6,6,-tetramethylpiperidin-1-oxyl, as described

in Tet. Asym., 2002, 13, 1201, to afford the carboxylic acid **1.5**.

Preparation of the BOC-protected aminohydroxy arylthiobutanoic acids 3.1.

10

Schemes **43** and **44** illustrate two alternative methods for the preparation of the BOC-

protected aminohydroxy arylthiobutanoic acids **3.1**. As shown in Scheme **43**, N, N-dibenzyl

serine methyl ester **43.1**, prepared as described in J. Org. Chem., 1986, 63, 1709, is converted

into the methanesulfonate ester **43.2**. The carbinol is reacted with methanesulfonyl chloride

15   and triethylamine in toluene, as described in J. Org. Chem., 65, 2000, 1623, to produce the

mesylate **43.2**. The latter compound is then reacted with a thiophenol R^6SH, in the presence of

a base, to give the thioether **43.4**. The displacement reaction is performed in an organic

solvent such as dimethylformamide, or in an aqueous organic solvent mixture, in the presence

of an organic base such as triethylamine or dimethylaminopyridine, or an inorganic base such

20   as potassium carbonate and the like. Preferably, the reactants are combined in toluene solution

in the presence of aqueous sodium hydroxide and a phase transfer catalyst such as tetrabutyl

ammonium bromide, as described in J. Org. Chem., 65, 2000, 1623, to afford the product

43.4. The ester product is then transformed into the corresponding aldehyde **43.5**, using the

procedures described above (Scheme **41**). The aldehyde is then converted, using the sequence

25   of reactions shown in Scheme **41**, into the BOC-protected aminohydroxy arylthiobutanoic

acids **3.1**.

Alternatively, as shown in Scheme **44**, the aldehyde **43.5** is converted, using the sequence of

reactions shown in Scheme **42**, into the product **3.1**. The component reactions of this

sequence are performed under similar conditions to those described for the analogous

30   reactions in Scheme **42**.

Preparation of phosphonate-containing hydroxymethyl benzoic acids 1.8.

Schemes **45 - 49** illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids **1.8** which are employed in the preparation of the phosphonate esters **1**.

5   Scheme **45** illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **45.1** is subjected to halogen-methyl exchange to afford the organometallic intermediate **45.2**. This compound is reacted with a chlorodialkyl phosphite **45.3** to yield the phenylphosphonate ester **45.4**, which upon deprotection affords the

10   carboxylic acid **45.5**.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **45.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **45.7**, as described in

15   Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **45.8**. This compound is treated with boron trifluoride at 0^0 to effect rearrangement to the orthoester **45.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **45.10**. Halogen-metal exchange is performed by the

20   reaction of the substrate **45.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **45.3**, to produce the phosphonate **45.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **45.12**.

25   Using the above procedures, but employing, in place of the bromo compound **45.6**, different bromo compounds **45.1**, there are obtained the corresponding products **45.5**.

Scheme **46** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

30   In this method, a suitably protected dimethyl hydroxybenzoic acid, **46.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **46.2** is reacted with a sodium dialkyl phosphite, **46.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect

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displacement of the benzylic bromide to afford the phosphonate **46.4**. Deprotection of the carboxyl function then yields the carboxylic acid **46.5**.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, **46.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described

5   in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **46.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **46.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford

10 the bromomethyl product **46.8**. This compound is then reacted with a sodium dialkyl phosphite **46.3** in tetrahydrofuran, as described above, to afford the phosphonate **46.9**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **46.10**. Using the above procedures, but employing, in place of the methyl compound **46.6**, different

15 methyl compounds **46.1**, there are obtained the corresponding products **46.5**.

Scheme **47** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic

20 acid **47.1** is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **47.2**, to afford the coupled product **47.3**, which upon deprotection affords the carboxylic acid **47.4**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **47.5**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **47.6**, by

25 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether **47.7**. This compound is then reacted

30 with a dialkyl hydroxymethylphosphonate **47.2**, under the conditions of the Mitsonobu reaction. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.

448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or

5   thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the coupled product **47.9**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **47.9**.

Using the above procedures, but employing, in place of the phenol **47.5**, different phenols or

10   thiophenols **47.1**, there are obtained the corresponding products **47.4**.

Scheme **48** depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains. In this method, a dialkyl alkenylphosphonate **48.2** is coupled, by means of a palladium

15   catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **48.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a

20   palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product **48.3** is deprotected to afford the phosphonate **48.4**; the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid **48.5**.

25   For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **48.6**, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **48.7**. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **48.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above to afford the product **48.9**. Deprotection, or hydrogenation/deprotection, of this compound, as

30   described above, then affords respectively the unsaturated and saturated products **48.10** and **48.11**.

Using the above procedures, but employing, in place of the bromo compound **48.6**, different bromo compounds **48.1**, and/or different phosphonates **48.2**, there are obtained the corresponding products **48.4** and **48.5**.

5   Scheme **49** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **49.1** is converted to the corresponding boronic acid **49.2**, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a

10   Suzuki coupling reaction with a dialkyl bromophenyl phosphonate **49.3**. The product **49.4** is then deprotected to afford the diaryl phosphonate product **49.5**.

For example, the silylated OBO ester **49.6**, prepared as described above, (Scheme 45), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp. Radiopharm., 1992, 31, 175, is converted into the boronic acid **49.7**, as described above. This

15   material is coupled with a dialkyl 4-bromophenyl phosphonate **49.8**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **49.9**. Deprotection, as described above, then affords the benzoic acid **49.10**.

20   Using the above procedures, but employing, in place of the bromo compound **49.6**, different bromo compounds **49.1**, and/or different phosphonates **49.3**, there are obtained the corresponding carboxylic acid products **49.5**.

Scheme 41
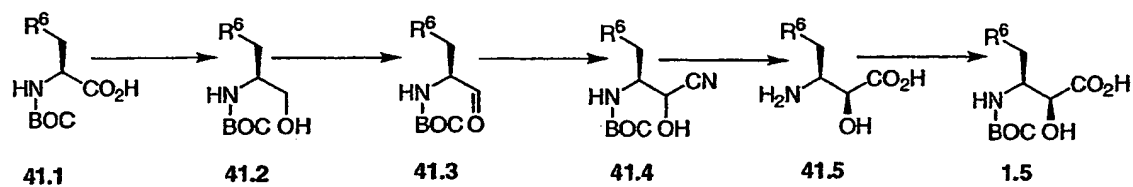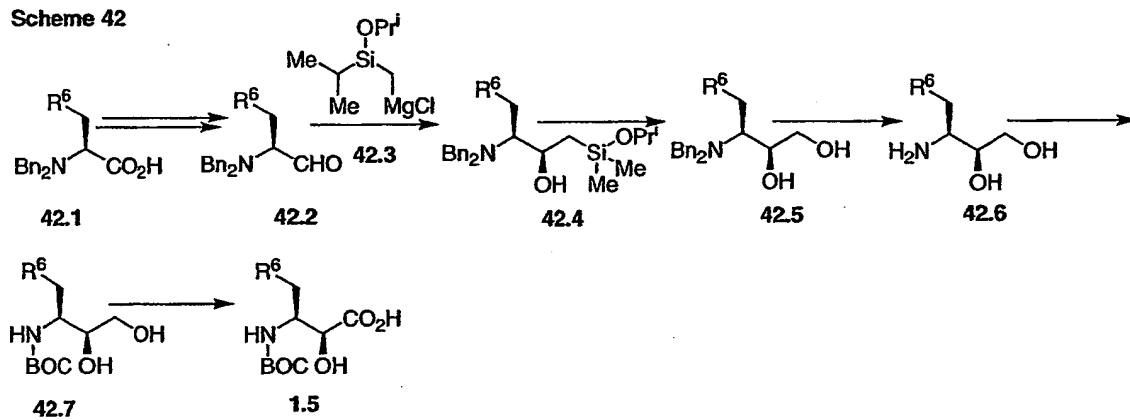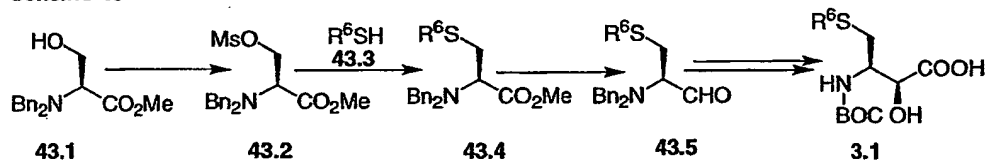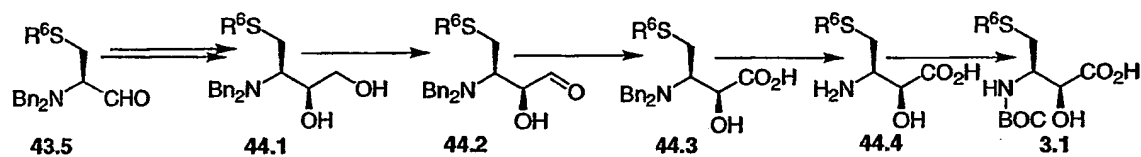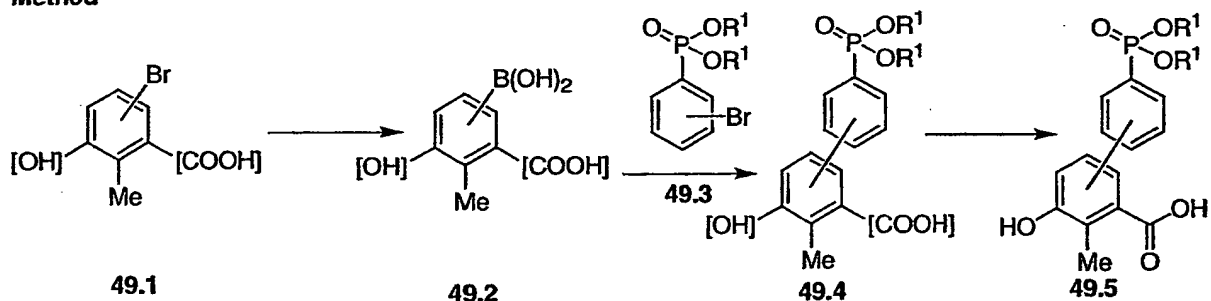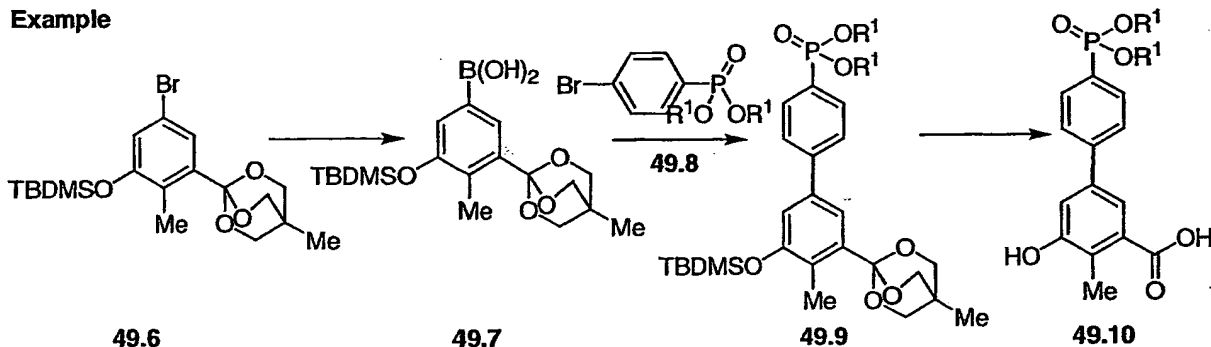
41.1   41.2   41.3   41.4   41.5   1.5

Scheme 42

42.1   42.2   42.3   42.4   42.5   42.6

42.7   1.5

Scheme 43

43.1   43.2   43.3   43.4   43.5   3.1

Scheme 44

43.5   44.1   44.2   44.3   44.4   3.1

Scheme 49
Method

49.1   49.2   **49.3**   49.4   49.5

Example

49.8

49.6   49.7   49.9   49.10

Preparation of dimethylphenoxyacetic acids 5.1 incorporating phosphonate moieties.

5   The preparation of the dimethylphenoxyacetic acids **5.1** incorporating phosphonate moieties which are used in the preparation of the phosphonate esters **2** is described in Schemes **50 - 56**.

Scheme **50** illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be

10   introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol **50.1**, in which the substituent B is a precursor to the group link-P(O)(OR^1)$_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions

15   to be performed, is converted into a phosphonate-containing compound **50.2**. Methods for the conversion of the substituent B into the group link-P(O)(OR^1)$_2$ are described in Schemes **46 - 101**.

The protected phenolic hydroxyl group present in the phosphonate-containing product **50.2** is then deprotected, using methods described below, to afford the phenol **50.3**.

The phenolic product **50.3** is then transformed into the corresponding phenoxyacetic acid

50.4, in a two step procedure. In the first step, the phenol **50.3** is reacted with an ester of

bromoacetic acid **50.4**, in which R is an alkyl group or a protecting group. Methods for the

protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by

5   T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of

phenols to afford phenolic ethers is described, for example, in Comprehensive Organic

Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the

alkylating agent are reacted together in the presence of an organic or inorganic base, such as,

for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent

10   such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **50.3** and ethyl bromoacetate are reacted together

in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described

in US Patent 5914332, to afford the ester **50.5**.

The thus-obtained ester **50.5** is then hydrolyzed to afford the carboxylic acid **50.6**. The

15   methods used for this reaction depend on the nature of the group R. If R is an alkyl group

such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous

alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a

protecting group, methods for hydrolysis are described in Protective Groups in Organic

Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

20   Preferably, the ester product **50.5** which R is ethyl is hydrolyzed to the carboxylic acid **50.6** by

reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in

US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **50.8**, in which the substituent B

is a precursor to the group link-P(O)(OR^1)$_2$, is transformed into the corresponding

25   phenoxyacetic ester **50.7**. The conditions employed for the alkylation reaction are similar to

those described above for the conversion of the phenol **50.3** into the ester **50.5**.

The phenolic ester **50.7** is then converted, by transformation of the group B into the group

link-P(O)(OR^1)$_2$ followed by ester hydrolysis, into the carboxylic acid **50.6**. The group B

which is present in the ester **50.6** may be transformed into the group link-P(O)(OR^1)$_2$ either

30   before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the

nature of the chemical transformations required.

Schemes **51** - **56** illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating

phosphonate ester groups. The procedures shown can also be applied to the preparation of

phenoxyacetic esters acids **50.7**, with, if appropriate, modifications made according to the

knowledge of one skilled in the art.

5

Scheme **51** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a

phosphonate ester which is attached to the phenolic group by means of a carbon chain

incorporating a nitrogen atom. The compounds **51.4** are obtained by means of a reductive

alkylation reaction between a 2,6-dimethylphenol aldehyde **51.1** and an aminoalkyl

10 phosphonate ester **51.2**. The preparation of amines by means of reductive amination

procedures is described, for example, in Comprehensive Organic Transformations, by R. C.

Larock, VCH, p. 421. In this procedure, the amine component **51.2** and the aldehyde

component **51.1** are reacted together in the presence of a reducing agent such as, for example,

borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product

15 **51.3**. The amination product **51.3** is then converted into the phenoxyacetic acid compound

51.4, using the alkylation and ester hydrolysis procedures described above, (Scheme **50**)

For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **51.5** (Aldrich) and a

dialkyl aminoethyl phosphonate **51.6**, the preparation of which is described in J. Org. Chem.,

2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic

20 acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the amine

product **51.7**. The product is then converted into the acetic acid **51.8**, as described above.

Using the above procedures, but employing, in place of the aldehyde **51.5**, different aldehydes

51.1, and/or different aminoalkyl phosphonates **51.2**, the corresponding products **51.4** are

obtained.

25

Scheme **52** depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group

linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this

procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **52.1** is coupled, by

means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **52.2**. The

30 coupling of aryl bromides with olefins by means of the Heck reaction is described, for

example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001,

p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as

dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst.
Following the coupling reaction, the product **52.3** is converted, using the procedures described
above, (Scheme **50**) into the corresponding phenoxyacetic acid **52.4**. Alternatively, the olefinic
product **52.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **52.5**. Methods

5   for the reduction of carbon-carbon double bonds are described, for example, in
Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods
include catalytic reduction, or chemical reduction employing, for example, diborane or
diimide. Following the reduction reaction, the product **52.5** is converted, as described above,
(Scheme **50**) into the corresponding phenoxyacetic acid **52.6**.

10   For example, 3-bromo-2,6-dimethylphenol **52.7**, prepared as described in Can. J. Chem.,
1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **52.8**, by reaction with
chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective
Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990
p. 77. The product **52.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate

15   **52.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of
bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce
the coupled product **52.10**. The silyl group is removed, for example by the treatment of the
ether **52.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in
J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **52.11**. This compound is converted,

20   employing the procedures described above, (Scheme **50**) into the corresponding phenoxyacetic
acid **52.12**. Alternatively, the unsaturated compound **52.11** is reduced, for example by
catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent
such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander,
Academic Press, 1985, Ch. 2, to afford the saturated analog **52.13**. This compound is

25   converted, employing the procedures described above, (Scheme **50**) into the corresponding
phenoxyacetic acid **52.14**.
Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **52.7**,
different bromophenols **52.1**, and/or different dialkyl alkenyl phosphonates **52.2**, the
corresponding products **52.4** and **52.6** are obtained.

30

Scheme **53** illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic
acids **53.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by

means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol 53.2 is converted, using the procedures illustrated in Scheme 50, into the corresponding 2,6-dimethylphenoxyacetic ester 53.3. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone 53.4, in which n is 1 or 2. The

5   coupling reaction is conducted under the same conditions as those described above for the preparation of the unsaturated phosphonate 52.3. (Scheme 52). The product 53.5 is then reduced catalytically, as described above for the reduction of the phosphonate 52.3, (Scheme 52), to afford the substituted cycloalkanone 53.6. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoalkylphosphonate 53.7 and sodium

10   triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate 53.8. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine 51.3 (Scheme 51). The resultant ester 53.8 is then hydrolyzed, as described above, to afford the phenoxyacetic acid 53.1.

For example, 4-bromo-2,6-dimethylphenol 53.9 (Aldrich) is converted, as described above,

15   into the phenoxy ester 53.10. The latter compound is then coupled, in dimethylformamide solution at ca. 60°, with cyclohexenone 53.11, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone 53.12. The enone is then reduced to the saturated ketone 53.13, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an

20   equimolar amount of a dialkyl aminoethylphosphonate 53.14, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine 53.15. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid 53.16.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol 53.9,

25   different bromo-substituted 2,6-dimethylphenols 53.2, and/or different cycloalkenones 53.4, and/or different dialkyl aminoalkylphosphonates 53.7, the corresponding products 53.1 are obtained.

Scheme 54 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a

30   phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol 54.1 is reacted, in the

presence of a base such as, for example, potassium carbonate, and optionally in the presence

of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl

phosphonate **54.2**. The reaction is conducted in a polar organic solvent such as

dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of

5   the alkylation reaction, **54.3** is then converted, as described above (Scheme **50**) into the

phenoxyacetic acid **54.4**.

For example, 2,6-dimethyl-4-mercaptophenol **54.5**, prepared as described in EP 482342, is

reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl

phosphonate **54.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the

10   presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product

54.7. This compound is converted, employing the procedures described above, (Scheme **50**)

into the corresponding phenoxyacetic acid **54.8**.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **54.5**,

different hydroxy, thio or aminophenols **54.1**, and/or different dialkyl bromoalkyl

15   phosphonates **54.2**, the corresponding products **54.4** are obtained.

Scheme 55 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a

phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this

procedure, an optionally protected hydroxy, mercapto or amino-substituted 2.6-

20   dimethylphenol **55.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or

heteroaryl compound **55.2**. Equimolar amounts of the phenol and the halomethyl compound

are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the

presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford

the ether, thioether or amino product **55.3**. The product **55.3** is then converted, using the

25   procedures described above, (Scheme **50**) into the phenoxyacetic ester **55.4**. The latter

compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **55.5**

at ca. 100° to afford the phosphonate ester **55.6**. The preparation of phosphonates by means of

the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992,

115. The resultant product **55.6** is then converted into the acetic acid **55.7** by hydrolysis of the

30   ester moiety, using the procedures described above, (Scheme **50**).

For example, 4-hydroxy-2,6-dimethylphenol **55.8** (Aldrich) is reacted with one molar

equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J.

Inorg. Chem., 1998, 2, 163, to afford the ether **55.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **55.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme **50**) to afford the phenoxyacetic ester **55.11**. This product is heated at 100° for 3

5   hours with three molar equivalents of triethyl phosphite **55.12**, to afford the phosphonate ester **55.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **55.14**.

Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **55.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **55.2**, and/or different

10   hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **55.1** and/or different trialkyl phosphites **55.5**, the corresponding products **55.7** are obtained.

Scheme **56** illustrates the preparation of dimethylphenoxyacetic acids incorporating a phosphonate group attached by mans of an amide group. In this procedure, a carboxy-

15   substituted 2,6-dimethylphenol **56.1** is reacted with a dialkyl aminoalkyl phosphonate **56.2** to afford the amide product **56.3**. The amide-forming reaction is performed under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**. The product **56.3** is then transformed, as described above (Scheme **50**) into the phenoxyacetic acid **56.4**. For example, 3,5-dimethyl-4-hydroxybenzoic acid **56.5** (Aldrich) is reacted with a dialkyl

20   aminoethylphosphonate **56.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in tetrahydrofuran solution in the presence of dicyclohexylcarbodiimide to produce the amide **56.7**. The product is then transformed, as described above, (Scheme **50**) into the corresponding phenoxyacetic acid **56.8**.

Using the above procedures, but employing, in place of 3,5-dimethyl-4-hydroxybenzoic acid

25   **56.5**, different carboxy-substituted 2,6-dimethylphenols **56.1**, and/or different dialkyl aminoalkyl phosphonates **56.2**, the corresponding products **56.4** are obtained.

Scheme 56
Method

56.1   56.3   56.4

Example

56.5   56.7   56.8
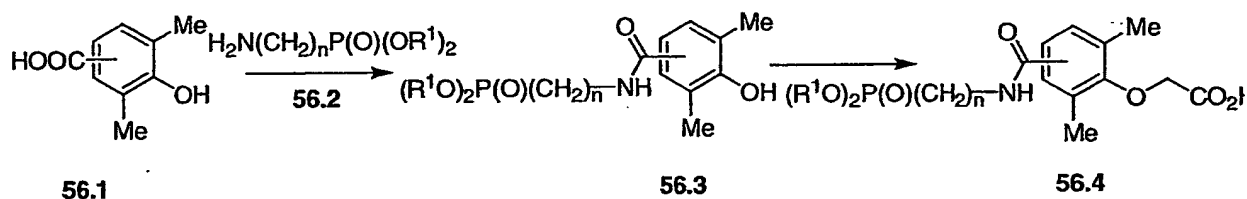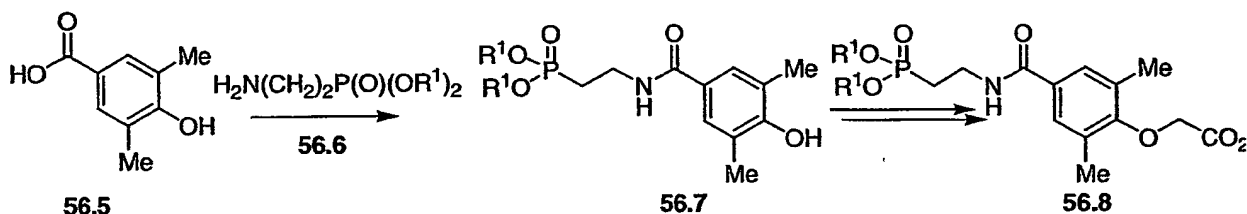
Preparation of quinoline 2-carboxylic acids 9.1 incorporating phosphonate moieties.

5   The reaction sequences depicted in Schemes **9 - 12** for the preparation of the phosphonate

esters **3** employ a quinoline-2-carboxylic acid reactant **9.1** in which the substituent A is either

the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or

are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino

10   and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het.

Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the

preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987,

109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures

known to those skilled in the art. The synthesis of variously substituted quinolines is described,

15   for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p

93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction,

which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed.,

Wiley, 1952, p. 204.

20   Scheme **57** illustrates the preparation of quinoline-2-carboxylic acids by means of the

Friedlander reaction, and further transformations of the products obtained. In this reaction

sequence, a substituted 2-aminobenzaldehyde **57.1** is reacted with an alkyl pyruvate ester **57.2**,

in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **57.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **57.4**. The carboxylic acid product **57.4** in which X is NH$_2$ can be further transformed into the corresponding compounds **57.6** in which Z is OH, SH

5   or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the

10   diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **57.6**, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic

15   Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **57.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol **57.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **57.3** instead

20   of the carboxylic acids **57.5**.

For example, 2,4-diaminobenzaldehyde **57.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **57.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **57.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the

25   carboxylic acid **57.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **57.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **57.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-

30   bromoquinoline-2-carboxylic acid **57.11**, Z = Br. Alternatively, the diazonium tetrafluoborate **57.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as

described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid
57.11, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **57.7**,
different aminobenzaldehydes **57.1**, the corresponding amino, hydroxy, bromo or mercapto-

5   substituted quinoline-2-carboxylic acids **57.6** are obtained. The variously substituted quinoline
carboxylic acids and esters can then be transformed, as described herein, (Schemes **58 – 60**)
into phosphonate-containing derivatives.

Scheme **58** depicts the preparation of quinoline-2-carboxylic acids incorporating a

10   phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In
this procedure, an amino-substituted quinoline-2-carboxylate ester **58.1** is transformed, via a
diazotization procedure as described above (Scheme **57**) into the corresponding phenol or
thiol **58.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate
58.3, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **58.4**.

15   The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for
example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448,
and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001,
p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an
aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl

20   azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **58.4**. Basic
hydrolysis of the ester group, for example employing one molar equivalent of lithium
hydroxide in aqueous methanol, then yields the carboxylic acid **58.5**. The product is then
coupled with a suitably protected aminoacid derivative **58.6** to afford the amide **58.7**. The
reaction is performed under similar conditions t those described above for the preparation of

25   the amide **1.6** (Scheme **1**). The ester protecting group is the removed to yield the carboxylic
acid **58.8**.

For example, methyl 6-amino-2-quinoline carboxylate **58.9**, prepared as described in J. Het.
Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above,
into methyl 6-mercaptoquinoline-2-carboxylate **58.10**. This material is reacted with a dialkyl

30   hydroxymethylphosphonate **58.11** (Aldrich) in the presence of diethyl azodicarboxylate and
triphenylphosphine in tetrahydrofuran solution, to afford the thioether **58.12**. Basic hydrolysis

then afford the carboxylic acid **58.13**. The latter compound is then converted, as described

above, into the aminoacid derivative **58.16**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline

carboxylate **58.9**, different aminoquinoline carboxylic esters **58.1**, and/or different dialkyl

5   hydroxymethylphosphonates **58.3** the corresponding phosphonate ester products **58.8** are

obtained.

Scheme **59** illustrates the preparation of quinoline-2-carboxylic acids incorporating

phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated

10   carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **59.1** is

coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate

59.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for

example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001,

p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as

15   dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as

tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II)

acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate.

Thus, Heck coupling of the bromo compound **59.1** and the olefin **59.2** affords the olefinic

ester **59.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or

20   by treatment with porcine liver esterase, then yields the carboxylic acid **59.4**. The latter

compound is then transformed, as described above, into the homolog **59.5**. Optionally, the

unsaturated carboxylic acid **59.4** can be reduced to afford the saturated analog **59.6**. The

reduction reaction can be effected chemically, for example by the use of diimide or diborane,

as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5,

25   or catalytically. The product **59.6** is then converted, as described above (Scheme **58**) into the

aminoacid derivative **59.7**.

For example, methyl 7-bromoquinoline-2-carboxylate, **59.8**, prepared as described in J.

Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a

dialkyl vinylphosphonate **59.9** (Aldrich) in the presence of 2 mol% of

30   tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **59.10**

The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the

carboxylic acid **59.11**. The latter compound is reacted with diimide, prepared by basic

hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **59.12**. The latter compound is then converted, as described above, into the aminoacid derivative **59.13**. The unsaturated product **59.11** is similarly converted into the analog **59.14**.

5   Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **59.8**, different bromoquinoline carboxylic esters **59.1**, and/or different dialkyl alkenylphosphonates **59.2**, the corresponding phosphonate ester products **59.5** and **59.7** are obtained.

10 Scheme **60** depicts the preparation of quinoline-2-carboxylic acid derivatives **60.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **60.1** is reacted with a phosphonate aldehyde **60.2** under reductive amination conditions, to afford the aminoalkyl product **60.3**. The preparation of amines by means of reductive amination procedures is described, for

15 example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in

20 the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **60.3** is then hydrolyzed to yield the free carboxylic acid **60.4**. The latter compound is then converted, as described above, into the aminoacid derivative **60.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **60.6**, prepared as described in J. Am.

25 Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **60.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **60.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **60.9**. The latter compound is then converted, as described above, into the aminoacid derivative **60.10**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **60.7**,

30 different formylalkyl phosphonates **60.2**, and/or different aminoquinolines **60.1**, the corresponding products **60.5** are obtained.

Preparation of 5-hydroxyisoquinoline derivatives 13.1 incorporating phosphonate moieties.

Schemes **61** - **65** illustrate methods for the preparation of the 5-hydroxyisoquinoline

5   derivatives **13.1** which are employed in the preparation of the intermediate phosphonate esters
4.

A number of substituted 5-hydroxyisoquinolines are commercially available, or have syntheses
described in the literature. The synthesis of substituted 5-hydroxyisoquinolines is described,
for example, in Heterocyclic Compounds, Vol. 38, Part 3, E. M. Coppola, H. F. Schuster,

10   eds., Wiley, 1995, p. 229ff, and in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992,
p. 162ff.

Scheme **61** illustrates methods for the preparation of substituted 5-hydroxyisoquinolines. As
shown in Method **1**, variously substituted 3-hydroxybenzaldehydes or 3-hydroxyphenyl

15   ketones **61.1** are reacted with substituted or unsubstituted 2, 2-dialkoxyethylamines **61.2** in a
procedure known as the Pomeranz-Fritsch reaction. The reactants are combined in a
hydrocarbon solvent such as toluene at reflux temperature with azeotropic removal of water,
to yield the imine product **61.3**. The latter compound is then subjected to acid-catalyzed
cyclization, for example as described in Heterocyclic Chemistry, by T. L. Gilchrist, Longman,

20   1992, p. 164, to yield the substituted 5-hydroxyisoquinoline **61.4**.
Scheme **61**, Method **2** illustrates the preparation of variously substituted 5-
hydroxyisoquinolines from the corresponding amino-substituted compounds. In this
procedure, a suitably protected amino-substituted 5-hydroxyisoquinoline **61.5** is subjected to a
diazotization reaction to afford the diazonium tetrafluoborate, using the conditions described

25   above in Scheme **57**. The diazonium salt is then converted, as described above, into the
corresponding hydroxy, mercapto or halo derivative **61.7**.

Scheme **62** illustrates the preparation of the isoquinolinyl-5-oxyacetic acids **62.2** and the
conversion of these compounds into the corresponding aminoacid derivatives **13.1**. In this

30   procedure, the 5-hydroxyisoquinoline substrate **62.1**, in which the substituent A is either the
group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH$_2$], Br, etc, as
described herein, is converted into the corresponding aryloxyacetic acid **62.2**. The procedures

employed for this transformation are the same as those described above, (Scheme 50) for the

conversion of 2,6-dimethoxyphenol derivatives into the corresponding phenoxyacetic acids.

The product 62.2 is then transformed, as described above, (Scheme 57) into the aminoacid

derivative 13.1.

5   Schemes 63 - 65 illustrate the preparation of 5-hydroxyisoquinoline derivatives incorporating

phosphonate substituents. The quinolinol products are then converted, as described above,

into analogs of the aminoacid derivative 13.1.

Scheme 63 illustrates the preparation of 5-hydroxyisoquinoline derivatives in which a

10   phosphonate substituent is attached by means of an amide bond. In this procedure, an amino-

substituted 5-hydroxyisoquinoline 63.1 is reacted with a dialkyl carboxyalkyl phosphonate

63.2 to afford the amide 63.3. The reaction is effected as described above for the preparation

of the amides 1.3 and 1.6.

For example, 8-amino-5-hydroxyisoquinoline 63.4, the preparation of which is described in

15   Syn. Comm., 1986, 16, 1557, is reacted in tetrahydrofuran solution with one molar equivalent

of a dialkyl 2-carboxyethyl phosphonate 63.5 (Epsilon) and dicyclohexyl carbodiimide, to

produce the amide 63.6.

Using the same procedures, but employing, in place of the 8-amino quinolinol 63.4, different

aminoquinolinols 63.1, and/or different dialkyl carboxyalkyl phosphonates 63.2, the

20   corresponding products 63.3 are obtained.

Scheme 64 illustrates the preparation of 5-hydroxyisoquinoline derivatives in which a

phosphonate substituent is attached by means of a carbon link or a carbon and a heteroatom

link. In this procedure, a methyl-substituted 5-hydroxyisoquinoline 64.1 is protected, and the

25   product 64.2 is reacted with a free radical brominating agent, for example N-

bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl

derivative 64.3. The latter compound is reacted with a trialkyl phosphite $(R^1O)_3P$ under the

conditions of the Arbuzov reaction, as described in Scheme 55, to yield the phosphonate 64.4;

deprotection then affords the phenol 64.5.

30   Alternatively, the protected bromomethyl derivative 64.3 is reacted with a dialkyl hydroxy,

mercapto or amino-substituted alkyl phosphonate 64.6, to afford the alkylation product 64.7.

The displacement reaction is conducted in a polar organic solvent such as dimethyl formamide,

acetonitrile and the like, in the presence of a base such as sodium hydride or lithium

hexamethyldisilazide, for substrates in which X is O, or potassium carbonate for substrates in

which X is S or N. The protecting group is then removed from the product **64.7** to yield the

phenolic product **64.8**.

5   For example, 5-hydroxy-1-methylisoquinoline **64.9**, prepared as described in J. Med. Chem.,

1968, 11, 700, is reacted with acetic anhydride in pyridine to afford 5-acetoxy-1-

methylisoquinoline **64.10**. The latter compound is reacted with N-bromosuccinimide in

refluxing ethyl acetate to yield 5-acetoxy-1-bromomethylisoquinoline **64.11**. The product is

then reacted with five molar equivalents of a trialkyl phosphite at 120° to give the phosphonate

10   product **64.12**. The acetoxy group is hydrolyzed by reaction with sodium bicarbonate in

aqueous methanol as described in J. Am. Chem. Soc., 93, 746, 1971, to produce the phenol

64.13.

Using the above procedures, but employing, in place of 5-hydroxy-1-methylisoquinoline **64.9**,

different hydroxymethylisoquinolines **64.1**, the corresponding products **64.5** are obtained.

15   As a further illustration of the method of Scheme **64**, as shown in Example 2, 5-hydroxy-3-

methylisoquinoline **64.14**, prepared as described in J. Med. Chem., 1998, 41, 4062, is reacted

with one molar equivalent of tert. butyl chlorodimethylsilane and imidazole in dichloromethane

to yield the silyl ether **64.15**. The product is brominated, as described above, to afford 3-

bromomethyl-5-tert. butyldimethylsilyloxyisoquinoline **64.16**. The bromomethyl compound is

20   then reacted in dimethylformamide at 60° with one molar equivalent of a dialkyl mercaptoethyl

phosphonate **64.17**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and

potassium carbonate, to give the thioether product **64.18**; deprotection, for example by

treatment with 1M tetrabutylammonium fluoride in tetrahydrofuran, then yields the phenol

64.19.

25   Using the above procedures, but employing, in place of 5-hydroxy-3-methylisoquinoline

64.11, different hydroxymethylisoquinolines **64.1**, and/or different hetero-substituted alkyl

phosphonates **64.6**, the corresponding products **64.8** are obtained.

Scheme **65** illustrates the preparation of 5-hydroxyisoquinoline derivatives incorporating a

30   phosphonate moiety attached by means of a heteroatom and an alkylene chain. In this

procedure, the phenolic hydroxyl group of 5-hydroxyisoquinolin-1-one **65.1** (Acros) is

protected. The protection of phenolic hydroxyl groups is described, for example, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

p. 143ff. The product **65.2** is then converted into the bromo analog **65.3**, for example by

reaction with phosphorus oxybromide, as described in Heterocyclic Compounds, Vol. 38, Part

2, E. M. Coppola, H. F. Schuster, eds., Wiley, 1995, p. 13ff. The bromo compound is then

5   reacted with a dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonate **65.4**, to

afford the displacement product **65.5**. The displacement reaction of 2-haloisoquinolines with

nucleophiles to produce ethers, thioethers and amines is described in Heterocyclic Chemistry,

by T. L. Gilchrist, Longman, 1992, p. 165. The reaction is conducted in an organic solvent

such as dimethylformamide, toluene and the like, in the presence of a base such as sodium

10   hydride or potassium carbonate. The phenolic hydroxyl group is then deprotected to yield the

phenol **65.6**.

For example, 5-hydroxyisoquinolin-1-one **65.1** is reacted with one molar equivalent of benzoyl

chloride in pyridine to afford the ester **65.7**. The latter compound is treated with phosphorus

oxybromide in refluxing toluene to produce the 5-benzoyloxy-1-bromoisoquinoline **65.8**. This

15   material is reacted with a dialkyl 3-hydroxypropyl phosphonate **65.9**, prepared as described in

Zh. Obschei. Khim., 1974, 44, 1834, and sodium hydride in tetrahydrofuran to prepare the

ether product **65.10**. Deprotection, for example by reaction with aqueous alcoholic sodium

bicarbonate, then yields the phenol **65.11**.

Using the above procedures, but employing, in place of a dialkyl 3-hydroxypropyl

20   phosphonate **65.9**, different dialkyl hydroxy, mercapto or amino-substituted alkyl

phosphonates **65.4**, the corresponding products **65.6** are obtained.

Scheme **66** described the preparation of 5-hydroxyisoquinolines in which a phosphonate

substituent is attached by means of a saturated or unsaturated alkylene chain. In this

25   procedure, a bromo-substituted 5-hydroxyisoquinoline **66.1** is protected, as described above.

The product **66.2** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl

phosphonate **66.3**. The coupling of aryl bromides and alkenes is described above (Scheme **52**).

The product **66.4** is then deprotected to yield the phenol **66.5**. Optionally, the compound **66.5**

is reduced, for example by treatment with diimide or diborane, to afford the saturated analog

30   **66.6**.

For example, 5-hydroxyisoquinoline **66.7** is reacted with bromine in carbon tetrachloride to

afford 8-bromo-5-hydroxyisoquinoline **66.8**. The product is reacted with acetic anhydride in

pyridine to give 5-acetoxy-8-bromoisoquinoline **66.9**. The latter compound is coupled with a

dialkyl propenyl phosphonate **66.10** (Aldrich) in the presence of ca. 3 mol % of

bis(triphenylphosphine) palladium(II) chloride and triethylamine, in dimethylformamide at ca.

60°, to produce the coupled product **66.11**. The acetyl protecting group is then removed by

5   reaction with dilute aqueous methanolic ammonia, as described in J. Chem. Soc., 2137, 1964,

to afford the phenol **66.12**. The product is optionally reduced to yield the saturated analog

66.13. The reduction reaction is effected chemically, for example by the use of diimide or

diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH,

1989, p. 5, or catalytically.

10   Using the above procedures, but employing, in place of 8-bromo-5-hydroxyisoquinoline **66.8**,

different bromo-substituted 5-hydroxyisoquinolines **66.1**, and/or different dialkyl alkenyl

phosphonates **66.3**, the corresponding products **66.5** and **66.6** are obtained.

Scheme 65
Method
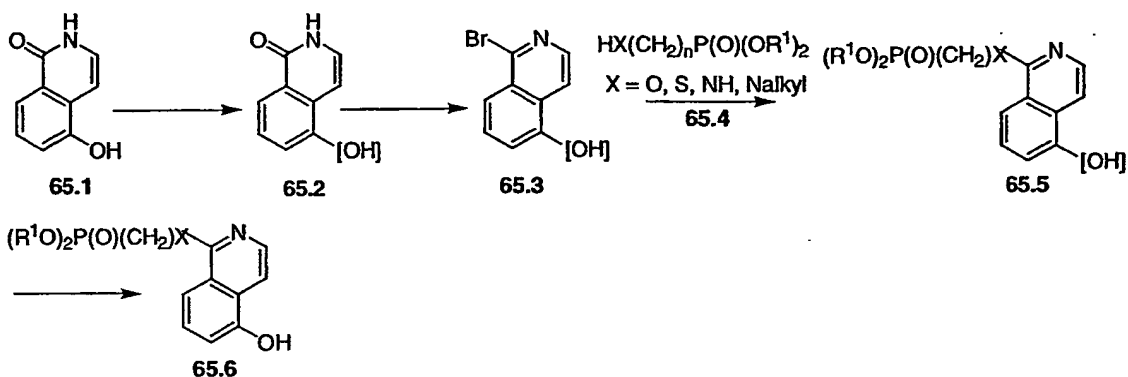
Example
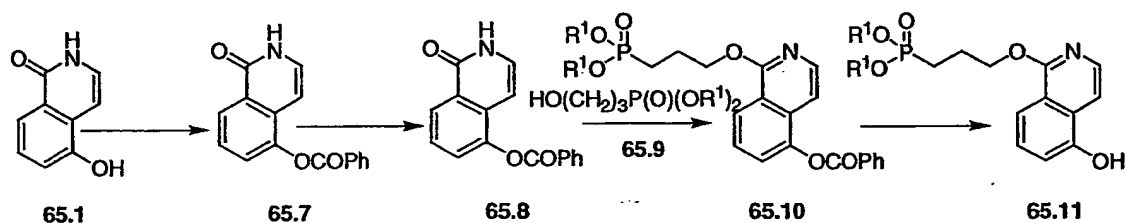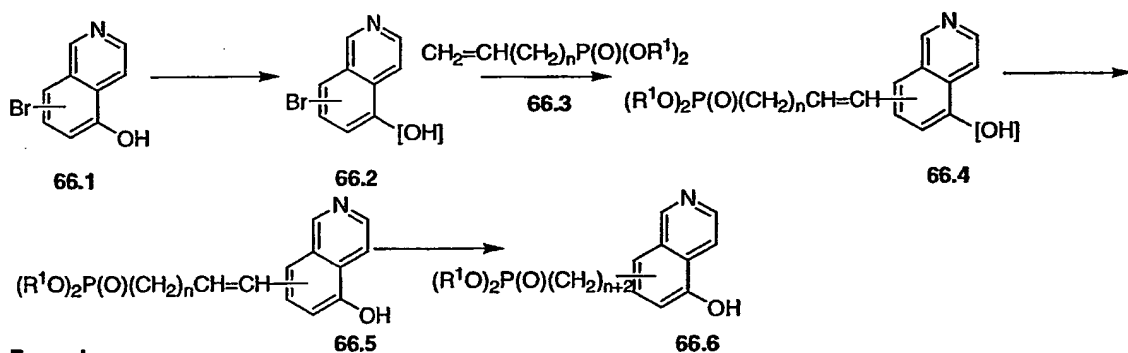
Scheme 66
Method

Example
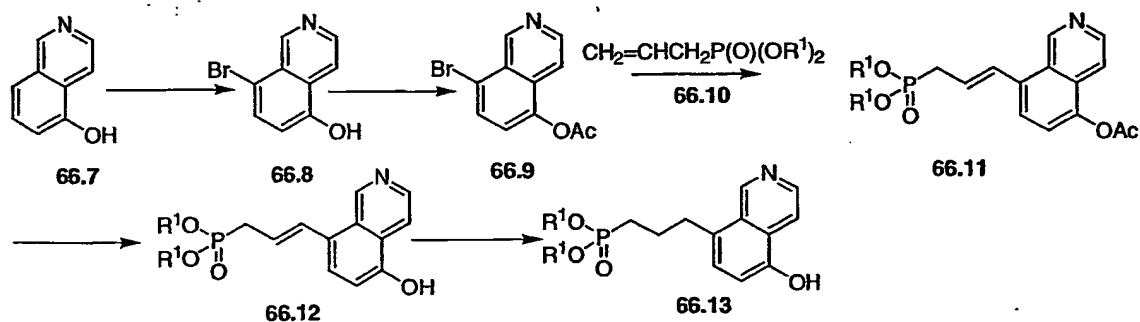
Preparation of phenylalanine derivatives 17.1 incorporating phosphonate moieties.

Schemes **67** - **71** illustrate the preparation of phosphonate-containing phenylalanine derivatives
17.1 which are employed in the preparation of the intermediate phosphonate esters **5**.

Scheme **67** illustrates the preparation of phenylalanine derivatives incorporating phosphonate

5   moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The
compounds are obtained by means of alkylation or condensation reactions of hydroxy or
mercapto-substituted phenylalanine derivatives **67.1**.
In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the
benzyl ester **67.2**. The conversion of carboxylic acids into esters is described for example, in

10   Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 966. The
conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid
and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a
benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in
the benzyl ester **67.2** is then protected. Protection methods for phenols and thiols are

15   described respectively, for example, in Protective Groups in Organic Synthesis, by T.W.
Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 10, p 277. For example, suitable
protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-
butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in
Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second

20   Edition 1990, p. 289 The protected hydroxy- or mercapto ester **67.3** is then converted into the
BOC derivative **67.4**. The protecting group present on the O or S substituent is then removed.
Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis,
by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p 277. For example, silyl
protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in

25   a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc.,
94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric
trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.
The resultant phenol or thiophenol **67.5** is then reacted under various conditions to provide
protected phenylalanine derivatives **67.9**, **67.10** or **67.11**, incorporating phosphonate moieties

30   attached by means of a heteroatom and an alkylene chain.
In this step, the phenol or thiophenol **67.5** is reacted with a dialkyl bromoalkyl phosphonate
67.6 to afford the ether or thioether product **67.9**. The alkylation reaction is effected in the

presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate, The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **67.9**. Deprotection of the benzyl ester group, for example by means

5   of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid **67.12**. The benzyl esters **67.10** and **67.11**, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme **67**, Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **67.13** is converted, as described above, into the benzyl ester **67.14**.

10   The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **67.15**. This compound is then converted, as described above, into the BOC derivative **67.16**. The silyl protecting group is removed by treatment of the silyl ether **67.16** with a tetrahydrofuran solution of tetrabutyl ammonium

15   fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **67.17**. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **67.18** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **67.19**. Debenzylation then produces the carboxylic acid **67.20**.

20   Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **67.13**, different hydroxy or thio-substituted phenylalanine derivatives **67.1**, and/or different bromoalkyl phosphonates **67.6**, the corresponding ether or thioether products **67.12** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **67.5**

25   is reacted with a dialkyl hydroxymethyl phosphonate **67.7** under the conditions of the Mitsonobu reaction, to afford the ether or thioether compounds **67.10**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p

30   153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **67.10**.

For example, as shown in Scheme **67**, Example 2, 3-mercaptophenylalanine **67.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **67.22**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem.

5   Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **67.23**. This compound is then converted, as described above for the preparation of the compound **67.4**, into the BOC-protected derivative **67.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **67.24** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **67.25**. The latter compound is reacted,

10   under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **67.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **67.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **67.27**.

       Using the above procedures, but employing, in place of the mercapto-substituted

15   phenylalanine derivative **67.21**, different hydroxy or mercapto-substituted phenylalanines **67.1**, and/or different dialkyl hydroxymethyl phosphonates **67.7**, the corresponding products **67.10** are obtained.

       Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **67.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **67.8** in which

20   Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **67.11**.

       For example, as illustrated in Scheme **67**, Example 3, 3-hydroxyphenylalanine **67.28** (Fluka) is converted, using the procedures described above, into the protected compound **67.29**. The

25   latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **67.30**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **67.31**. Debenzylation then produces the carboxylic acid **67.32**.

       Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine

30   derivative **67.28**, different hydroxy or mercapto-substituted phenylalanines **67.1**, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates **67.8**, the corresponding products **67.11** are obtained.

Scheme **68** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a

5   formyl-substituted tribenzylated phenylalanine derivative **68.3** and a dialkyl aminoalkylphosphonate **68.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **68.1** is converted, as described above, into the BOC protected benzyl ester **68.2**. The latter compound is then oxidized to afford the corresponding aldehyde **68.3**. The conversion of alcohols to aldehydes is described,

10   for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **68.3**. For example, the carbinol **68.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the

15   aldehyde **68.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **68.4** in the presence of a suitable reducing agent to afford the amine product **68.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this

20   procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **68.6**.

25   For example, 3-(hydroxymethyl)-phenylalanine **68.7**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **68.8**. This compound is then reacted with a dialkyl aminoethylphosphonate **68.9**, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **68.10**, which is then deprotected to give

30   the carboxylic acid **68.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **68.7**, different hydroxymethyl phenylalanines **68.1**, and/or different aminoalkyl phosphonates **68.4**, the corresponding products **68.6** are obtained.

5   Scheme **69** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **69.1** is converted, as described above, (Scheme **68**) into the protected derivative **69.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **69.3** to produce the phosphonate ester **69.4**. The preparation of arylphosphonates by means of

10   a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid **69.5**. For example, 3-bromophenylalanine **69.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **68**) into the protected compound **69.7**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **69.8**,

15   triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **69.9**. Debenzylation then yields the carboxylic acid **69.10**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **69.6**, different bromophenylalanines **69.1**, and/or different dialkylphosphites **69.3**, the corresponding products

20   **69.5** are obtained.

Schemes **70** and **71** illustrate two methods for the conversion of the compounds **70.1**, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, into the homologated derivatives **17.1** which are employed in the preparation of

25   the intermediate phosphonate esters **5**.

As shown in Scheme **70**, the BOC-protected phenylalanine derivative **70.1** is converted, using the procedures described above in Scheme **41**, into the aldehyde **70.2**. The aldehyde is then converted, via the cyanohydrin **70.3**, into the homologated derivative **17.1**. The reaction sequence and conditions employed are the same as shown in Scheme **41** for the conversion of

30   the BOC-protected aminoacid **41.1** into the homologated derivative **1.5**.

Alternatively, as illustrated in Scheme **71**, the BOC-protected aminoacid **70.1** is deprotected to afford the amine **71.1**. The product is then converted, as described in Scheme **42**, into the

dibenzylated product **71.2**. The latter compound is then transformed, using the sequence of reactions and conditions shown in Scheme **42** for the conversion of the dibenzylated aminoacid **42.1** into the hydroxyacid **1.5**, into the homologated derivative **17.1**.

Scheme 70
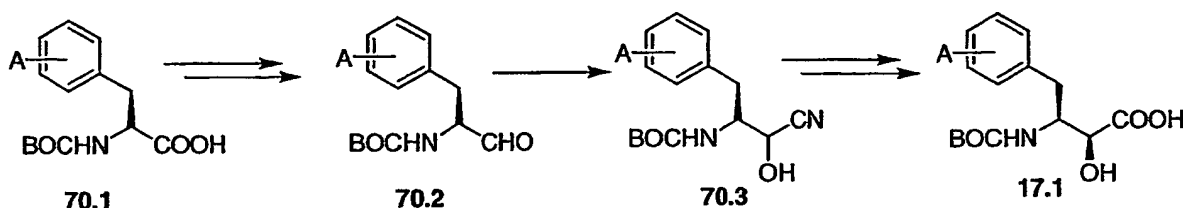
Scheme 71
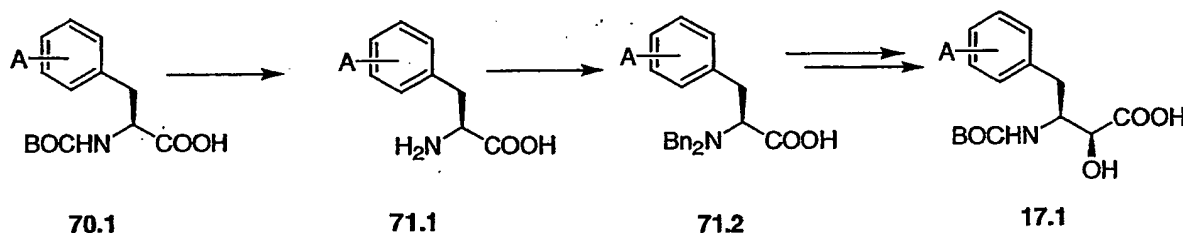
Preparation of the phosphonate-containing thiophenol derivatives 19.1.

Schemes **72 - 83** describe the preparation of phosphonate-containing thiophenol derivatives **19.1** which are employed as described above (Schemes **19** and **20**) in the preparation of the phosphonate ester intermediates **5** in which X is sulfur. Schemes **72 - 81** described the syntheses of the thiophenol components; Schemes **82** and **83** described methods for the incorporation of the thiophenols into the reactants **19.1**.

Scheme **72** depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol **72.1** is protected, as described above (Scheme **67**) to afford the protected product **72.2**. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **72.3**, to afford the phosphonate ester **72.4**. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described above, (Scheme **69**). The thiol protecting group is then removed, as described above, to afford the thiol **72.5**.

For example, 3-bromothiophenol 72.6 is converted into the 9-fluorenylmethyl (Fm) derivative 72.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 72.3, as described for the preparation of the phosphonate

5   69.4 (Scheme 69), to afford the phosphonate ester 72.8. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 72.9. Using the above procedures, but employing, in place of 3-bromothiophenol 72.6, different thiophenols 72.1, and/or different dialkyl phosphites 72.3, the corresponding products 72.5 are

10   obtained.

Scheme 73 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 73.2 is metallated, for example by reaction with magnesium or by transmetallation with an

15   alkyllithium reagent, to afford the metallated derivative 73.3. The latter compound is reacted with a halodialkyl phosphite 73.4 to afford the product 73.5; deprotection then affords the thiophenol 73.6

For example, 4-bromothiophenol 73.7 is converted into the S-triphenylmethyl (trityl) derivative 73.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

20   P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative 73.9 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite 73.10 to afford the phosphonate 73.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 73.12.

25   Using the above procedures, but employing, in place of the bromo compound 73.7, different halo compounds 73.1, and/or different halo dialkyl phosphites 73.4, there are obtained the corresponding thiols 73.6.

Scheme 74 illustrates the preparation of phosphonate-substituted thiophenols in which the

30   phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 74.1 is subjected to free-radical bromination to afford a bromomethyl product 74.2. This compound is reacted with a sodium dialkyl phosphite 74.3

or a trialkyl phosphite, to give the displacement or rearrangement product **74.4**, which upon deprotection affords the thiophenol **74.5**.

For example, 2-methylthiophenol **74.6** is protected by conversion to the benzoyl derivative **74.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M.

5 _ Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **74.8**. This material is reacted with a sodium dialkyl phosphite **74.3**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **74.9**. Alternatively, the bromomethyl compound **74.8** is converted into the phosphonate **74.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem.,

10 1992, 115. In this procedure, the bromomethyl compound **74.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0 to produce the phosphonate **74.9**. Deprotection of the phosphonate **74.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **74.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **74.8**,

15 different bromomethyl compounds **74.2**, there are obtained the corresponding thiols **74.5**.

Scheme 75 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **75.1** is reacted with a dialkyl hydroxyalkylphosphonate **75.2** under

20 the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **75.3**. Deprotection then yields the O- or S-linked products **75.4**.

For example, the substrate 3-hydroxythiophenol, **75.5**, is converted into the monotrityl ether **75.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is

25 reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **75.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **75.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **75.9**.

Using the above procedures, but employing, in place of the phenol **75.5**, different phenols or

30 thiophenols **75.1**, there are obtained the corresponding thiols **75.4**.

Scheme 76 illustrates the preparation of thiophenols 76.4 bearing a phosphonate group linked
to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O,
S or N-substituted thiophenol 76.1 is reacted with an activated ester, for example the
trifluoromethanesulfonate 76.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled

5   product 76.3. Deprotection then affords the thiol 76.4.

For example, 4-methylaminothiophenol 76.5 is reacted in dichloromethane solution with one
equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in
Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-
acetyl product 76.6. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl

10   phosphonate 76.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to
afford the displacement product 76.8. Preferably, equimolar amounts of the phosphonate 76.7
and the amine 76.6 are reacted together in an aprotic solvent such as dichloromethane, in the
presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate
product 76.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide

15   for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the
thiophenol 76.9.

Using the above procedures, but employing, in place of the thioamine 76.5, different phenols,
thiophenols or amines 76.1, and/or different phosphonates 76.2, there are obtained the
corresponding products 76.4.

20

Scheme 77 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by
means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement
reaction on a dialkyl bromoalkyl phosphonate 77.2. In this procedure, a suitably protected
hydroxy, thio or amino substituted thiophenol 77.1 is reacted with a dialkyl bromoalkyl

25   phosphonate 77.2 to afford the product 77.3. Deprotection then affords the free thiophenol
77.4.

For example, 3-hydroxythiophenol 77.5 is converted into the S-trityl compound 77.6, as
described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl
phosphonate 77.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction

30   is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a
base such as potassium carbonate, and optionally in the presence of a catalytic amount of

potassium iodide, at about 50°, to yield the ether product **77.8**. Deprotection, as described above, then affords the thiol **77.9**.

Using the above procedures, but employing, in place of the phenol **77.5**, different phenols, thiophenols or amines **77.1**, and/or different phosphonates **77.2**, there are obtained the

5   corresponding products **77.4**.

Scheme **78** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **78.2** is

10   coupled with an aromatic bromo compound **78.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as

15   tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **78.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **78.4**, or the saturated analog **78.6**.

20   For example, 3-bromothiophenol is converted into the S-Fm derivative **78.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **78.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar

25   solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **78.9**. Deprotection, as described above, then affords the thiol **78.10**. Optionally, the initially formed unsaturated phosphonate **78.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **78.11**, which upon deprotection affords the thiol **78.12**.

30   Using the above procedures, but employing, in place of the bromo compound **78.7**, different bromo compounds **78.1**, and/or different phosphonates **78.2**, there are obtained the corresponding products **78.4** and **78.6**

Scheme **79** illustrates the preparation of an aryl-linked phosphonate ester **79.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock,

5   VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **79.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **79.3** which is deprotected to yield the thiol **79.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane,

10 in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **79.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **79.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the

15 presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **79.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **79.8**.

Using the above procedures, but employing, in place of the boronate **79.5**, different boronates **79.1**, and/or different phosphonates **79.2**, there are obtained the corresponding products **79.4**.

20 Scheme **80** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **80.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **80.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a

25 bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **80.3** is then deprotected to afford the thiol **80.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **80.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **80.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **80.6**, the preparation of which is

30 described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The

thioether product **80.7** thus obtained is deprotected, as described above, to afford the thiol **80.8**.

Using the above procedures, but employing, in place of the thiophenol **80.5**, different phenols, thiophenols or amines **80.1**, and/or different phosphonates **80.2**, there are obtained the

5 corresponding products **80.4**.

Scheme **81** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **81.1**, for example an indoline (in which X-Y

10 is (CH$_2$)$_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH$_2$)$_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **81.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **81.3**. Deprotection, as described above, then affords the thiol **81.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted

15 indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of

20 hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic

25 Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707. For example, 2,3-dihydro-1H-indole-5-thiol, **81.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **81.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **81.7**, using the conditions described above for the preparation of the phosphonate **76.8**, (Scheme **76**), to yield the phosphonate **81.8**.

30 Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **81.9**.

Using the above procedures, but employing, in place of the thiol **81.5**, different thiols **81.1**, and/or different triflates **81.2**, there are obtained the corresponding products **81.4**.

Schemes **82** and **83** illustrate alternative methods for the conversion of the thiophenols **82.1**, in

5   which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, prepared as described above, (Schemes **72 – 81**) in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, into the homologated derivatives **19.1** which are employed in the preparation of the intermediate phosphonate esters **5** in which X is sulfur.

10   As shown in Scheme **82**, the thiophenol **82.1** is reacted with the mesylate ester **43.2**, using the conditions described above for the preparation of the thioether **43.4**, to afford the corresponding thioether **82.2**. The latter compound is then transformed, using the same sequence of reactions and reaction conditions described above (Scheme **43**) for the conversion of the thioether **43.4** into the hydroxyacid **3.1**, into the hydroxyacid **19.1**.

15   Alternatively, as shown in Scheme **83**, the aldehyde **82.3** is converted, as shown in Scheme **44**, into the diol **83.1**. The latter compound is then converted, as shown in Scheme **44** into the hydroxyacid **19.1**.

Scheme 81

Method

81.1
81.2
81.3
81.4

X-Y = (CH$_2$)$_2$,3 ; CH=CH

Example

81.5　　81.6　81.7　81.8　　81.9

Scheme 82

43.2　　82.1　82.2　　82.3　　19.1

Scheme 83

82.3　　83.1　　19.1
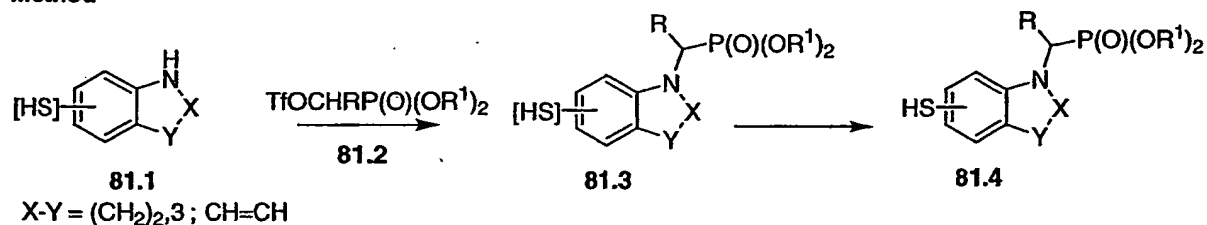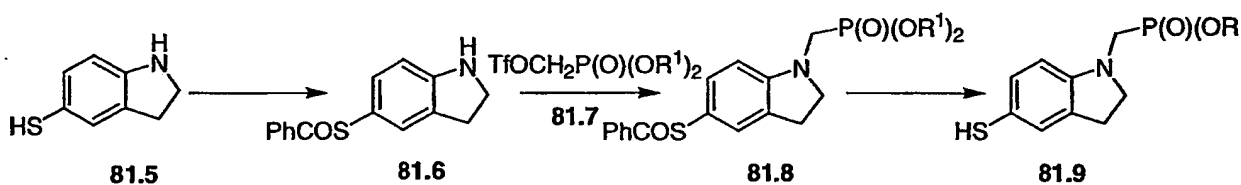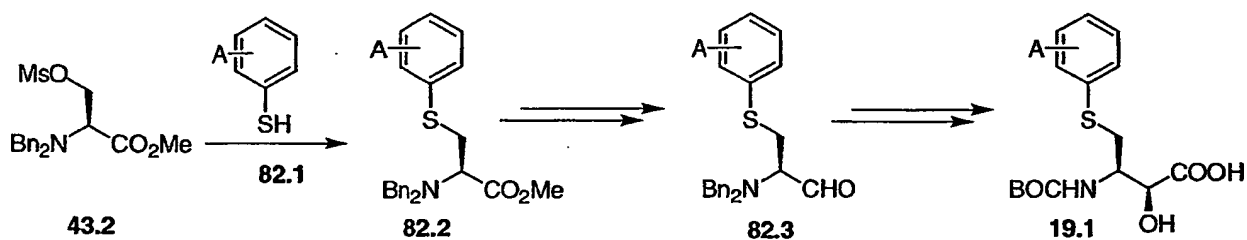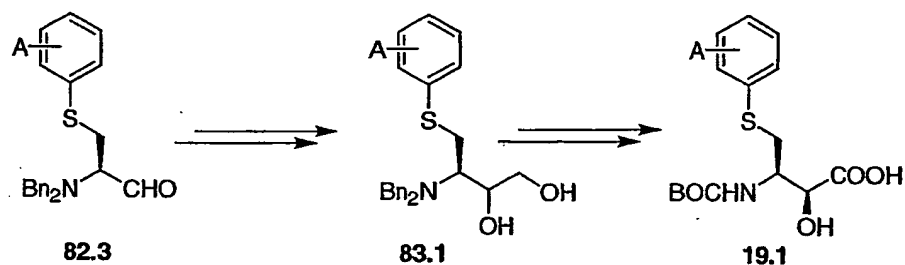
Preparation of tert-butylamine derivatives 25.1 incorporating phosphonate groups.

5　　Schemes **84 – 87** illustrate the preparation of the tert. butylamine derivatives **25.1** in which the substituent A is either the group link P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters **7**.

Scheme **84** describes the preparation of tert-butylamines in which the phosphonate moiety is
10　　directly attached to the tert-butyl group. A suitably protected 2.2-dimethyl-2-aminoethyl

bromide **84.1** is reacted with a trialkyl phosphite **84.2**, under the conditions of the Arbuzov

reaction, as described above, to afford the phosphonate **84.3**, which is then deprotected as

described previously to give **84.4**

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **84.6**, is heated with a

5   trialkyl phosphite at ca 150° to afford the product **84.7**. Deprotection, as previously described,

then affords the free amine **84.8**.

Using the above procedures, but employing different trisubstituted phosphites, there are

obtained the corresponding amines **84.4**.

10   Scheme **85** illustrates the preparation of phosphonate esters attached to the tert butylamine by

means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol **85.1** is

reacted with a bromoalkylphosphonate **85.2,** to afford the displacement product **85.3**.

Deprotection, if needed, then yields the amine **85.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **85.5** is reacted with a dialkyl

15   4-bromobutyl phosphonate **85.6**, prepared as described in Synthesis, 1994, 9, 909, in

dimethylformamide containing potassium carbonate and a catalytic amount of potassium

iodide, at ca 60° to afford the phosphonate **85.7** Deprotection, by hydrogenation over a

palladium catalyst, then affords the free amine **85.8**.

Using the above procedures, but employing different alcohols or thiols **85.1**, and/or different

20   bromoalkylphosphonates **85.2**, there are obtained the corresponding ether and thioether

products **85.4**.

Scheme **86** describes the preparation of carbon-linked tert. butylamine phosphonate

derivatives, in which the carbon chain can be unsaturated or saturated.

25   In the procedure, a terminal acetylenic derivative of tert-butylamine **86.1** is reacted, under

basic conditions, with a dialkyl chlorophosphite **86.2**, to afford the acetylenic phosphonate

86.3. The coupled product **86.3** is deprotected to afford the amine **86.4**. Partial or complete

catalytic hydrogenation of this compound affords the olefinic and saturated products **86.5** and

86.6 respectively.

30   For example, 2-amino-2-methylprop-1-yne **86.7**, the preparation of which is described in WO

9320804, is converted into the N-phthalimido derivative **86.8**, by reaction with phthalic

anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite **86.2** to afford the phosphonate **86.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **86.10**. Partial

5   catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate **86.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **86.12**.

10   Using the above procedures, but employing different acetylenic amines **86.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **86.4**, **86.5** and **86.6**.

Scheme **87** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

15   In this method, an aminoethyl-substituted cyclic amine **87.1** is reacted with a limited amount of a bromoalkyl phosphonate **87.2**, using, for example, the conditions described above (Scheme **78**) to afford the displacement product **87.3**.
     For example, 3-(1-amino-1-methyl)ethylpyrrolidine **87.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-

20   bromobutyl phosphonate **87.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **87.6**.
     Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine **87.4**, different cyclic amines **87.1**, and/or different bromoalkylphosphonates **87.2**, there are obtained the corresponding products **87.3**.

25

Scheme 86
Method

86.1   86.2   86.3   86.4

86.5   86.6

Example

86.7   86.8   phth = phthalimido   86.9   86.10

86.11   86.12

Scheme 87
Method

87.1   87.2   87.3

Example

87.4   87.5   87.6
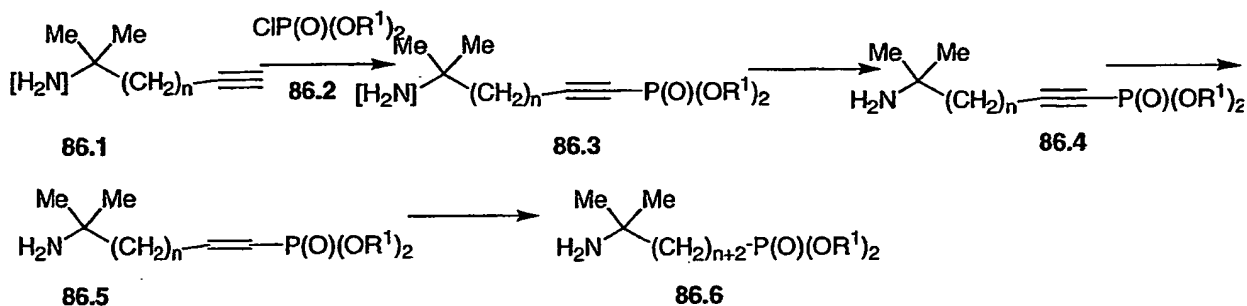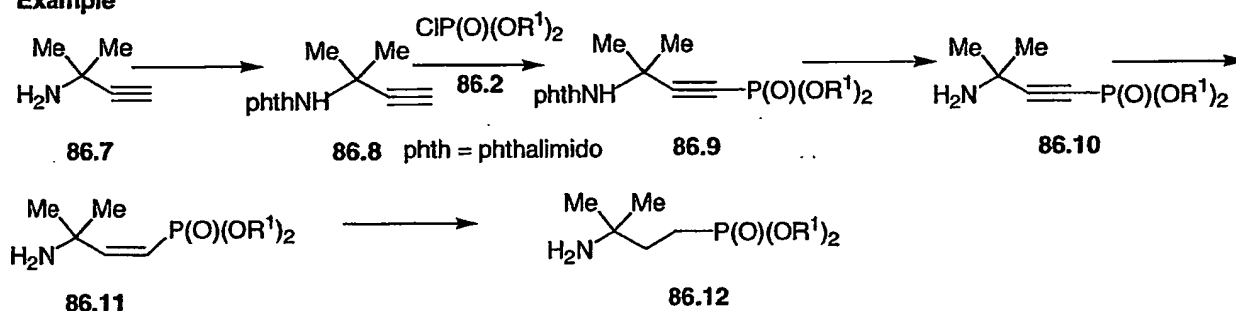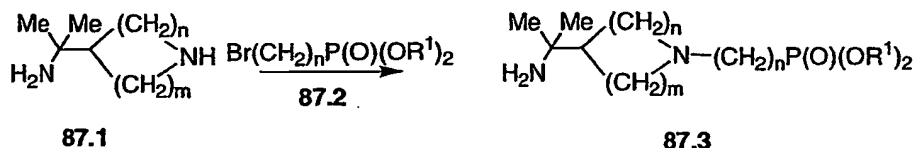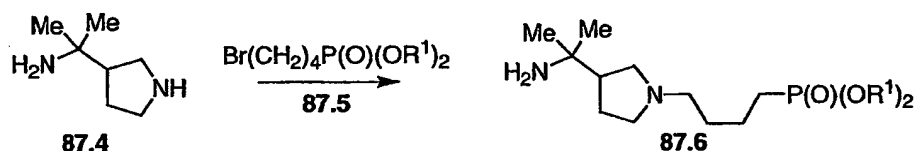
Preparation of phosphonate-containing methyl-substituted benzylamines 29.1.

5   Schemes **88 – 90** illustrate the preparation of phosphonate-containing 2-methyl and 2,6-dimethylbenzylamines **29.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the phosphonate ester intermediates **8**, as described in Schemes **29 – 32**. A number of variously substituted 2-methyl and 2,6-dimethylbenzylamies are commercially available or have

10   published syntheses. In addition, substituted benzylamines are prepared by various methods

known to those skilled in the art. For example, substituted benzylamines are obtained by reduction of the correspondingly substituted benzamides, for example by the use of diborane or lithium aluminum hydride, as described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 432ff.

5

Scheme 88 depicts the preparation of 2-methyl or 2,6-dimethylbenzyamines incorporating a phosphonate moiety directly attached to the benzene ring, or attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted 2-methyl or 2,6-dimethylbenzylamine 88.1 is protected to produce the analog 88.2. The protection of amines is

10   described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309ff. For example, the amine 88.1 is protected as an amide or carbamate derivative. The protected amine is then reacted with a dialkyl phosphite 88.3, in the presence of a palladium catalyst, as described above (Scheme 69) to afford the phosphonate product 88.4. Deprotection then affords the free amine 88.5.

15   Alternatively, the protected bromo-substituted benzylamine 88.2 is coupled with a dialkyl alkenyl phosphonate 88.6, using the conditions of the Heck reaction, as described above, (Scheme 59) to afford the alkenyl product 88.7. The amino protecting group is then removed to yield the free amine 88.8. Optionally, the olefinic double bond is reduced, for example by the use of diborane or diimide, or by means of catalytic hydrogenation, as described above

20   (Scheme 59) to produce the saturated analog 88.9.

For example, 4-bromo-2,6-dimethylbenzylamine 88.10, (Trans World Chemicals) is converted into the BOC derivative 88.11, as described above, and the product is coupled with a dialkyl phosphite 88.3, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phosphonate ester 88.12.

25   Deprotection, for example by treatment with trifluoroacetic acid, then produces the free amine 88.13.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylbenzylamine 88.10, different bromobenzylamines 88.1, the corresponding products 88.5 are obtained.

As an additional example of the methods of Scheme 88, 4-bromo-2-methylbenzylamine 88.14

30   (Trans World Chemicals) is converted into the BOC derivative 88.15. The latter compound is then reacted with a dialkyl vinylphosphonate 88.16, (Aldrich) in the presence of 2 mol % of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 88.17.

Deprotection then affords the amine **88.18**, and reduction of the latter compound with diimide gives the saturated analog **88.19**.

Using the above procedures, but employing, in place of 4-bromo-2-methylbenzylamine **88.14**, different bromobenzylamines **88.1**, and/or different alkenyl phosphonates **88.6**, the

5   corresponding products **88.8** and **88.9** are obtained.

Scheme **89** depicts the preparation of 2-methyl or 2,6-dimethylbenzyamines incorporating a phosphonate moiety attached to the benzene ring by means of an amide linkage. In this procedure, the amino group of a carboxy-substituted 2-methyl or 2,6-dimethylbenzylamine

10   **89.1** is protected to yield the product **89.2**. The latter compound is then reacted with a dialkyl aminoalkyl phosphonate **89.3** to afford the amide **89.4**. The reaction is performed as described above for the preparation of the amides **1.3** and **1.6**. The amine protecting group is then removed to give the free amine **89.5**.

For example, 4-carboxy-2-methylbenzylamine **89.6**, prepared as described in Chem. Pharm.

15   Bull., 1979, 21, 3039, is converted into the BOC derivative **89.7**. This material is then reacted in tetrahydrofuran solution with one molar equivalent of a dialkyl aminoethyl phosphonate **89.8**, in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, to produce the amide **89.9**. Deprotection, for example by reaction with methanesulfonic acid in acetonitrile, then yields the amine **89.10**.

20   Using the above procedures, but employing, in place of 4-carboxy-2-methylbenzylamine **89.6**, different carboxy-substituted benzylamines **89.1**, and/or different aminoalkyl phosphonates **89.3**, the corresponding products **89.5** are obtained.

Scheme **90** depicts the preparation of 2-methyl or 2,6-dimethylbenzyamines incorporating a

25   phosphonate moiety attached to the benzene ring by means of a heteroatom and an alkylene chain. In this procedure, the amino group of a hydroxy or mercapto-substituted methylbenzylamine **90.1** is protected to afford the derivative **90.2**. This material is then reacted with a dialkyl bromoalkyl phosphonate **90.3** to yield the ether or thioether product **90.4**. The reaction is conducted in a polar organic solvent such as dimethylformamide or N-

30   methylpyrrolidinone, in the presence of a base such as diazabicyclononene or cesium carbonate. The amino protecting group is then removed to afford the product **90.5**.

For example, 2,6-dimethyl-4-hydroxybenzylamine **90.6**, prepared, as described above, from 2,6-dimethyl-4-hydroxybenzoic acid, the preparation of which is described in J. Org. Chem., 1985, 50, 2867, is protected to afford the BOC derivative **90.7**. The latter compound is then reacted with one molar equivalent of a dialkyl bromoethyl phosphonate **90.8**, (Aldrich) and

5   cesium carbonate in dimethylformamide solution at 80° to give the ether **90.9**. Deprotection then afford the amine **90.10**.

Using the above procedures, but employing, in place of 4-hydroxy-2,6-dimethylbenzylamine **90.6**, different hydroxy or mercapto-substituted benzylamines **90.1**, and/or different bromoalkyl phosphonates **90.3**, the corresponding products **90.5** are obtained.

10

Scheme 89

Method

R = H, Me
89.1

89.2

89.4

89.5

Example

89.6

89.7

89.9

89.10

Scheme 90

Method

R = H, Me X = O, S
90.1

90.2

90.4

90.5

Example

90.6

90.7

90.9

90.10
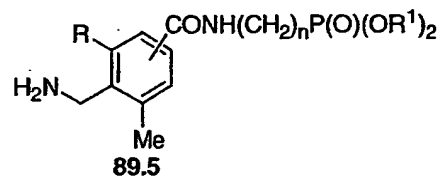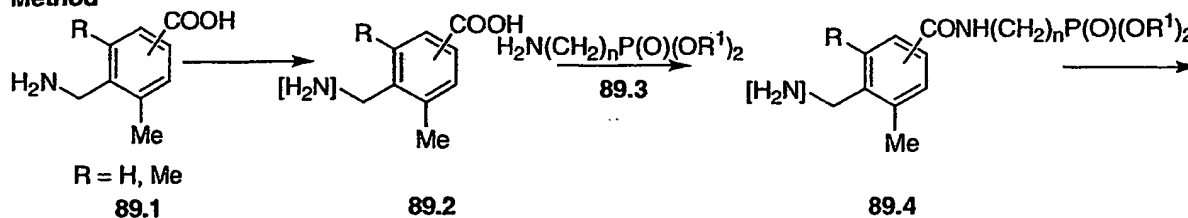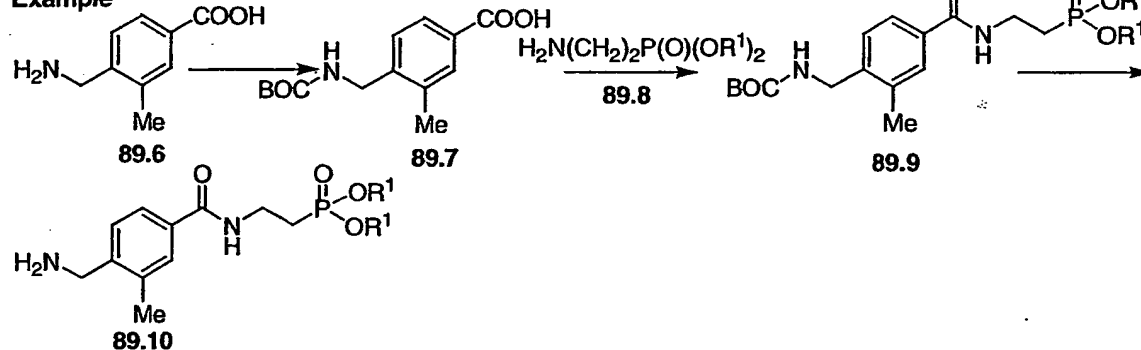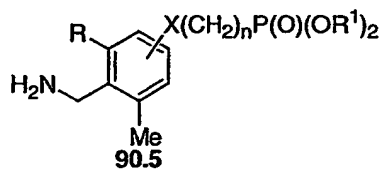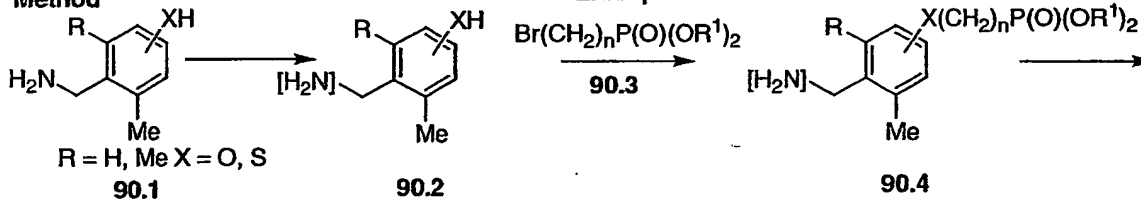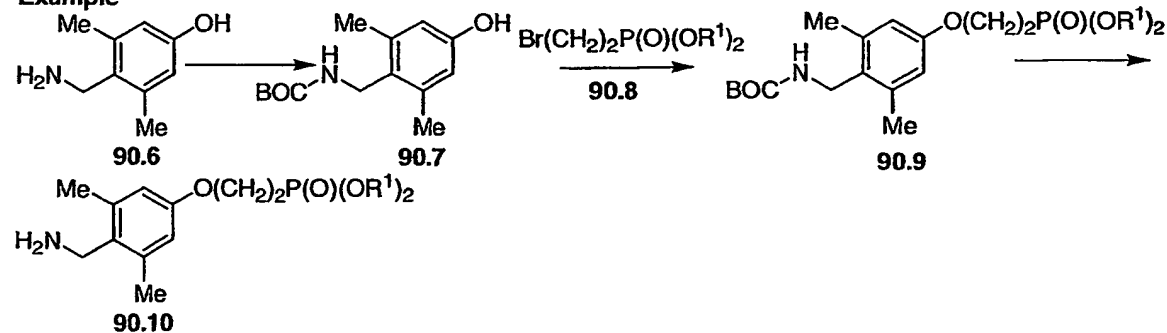
Preparation of phosphonate-substituted decahydroquinolines 33.1.

Schemes **91 – 97** illustrate the preparation of decahydroisoquinoline derivatives **33.1** in which

5   the substituent A is either the group link P(O)(OR^1)$_2$ or a precursor thereto, such as [OH],

[SH], Br etc. The compounds are employed in the preparation of the intermediate

phosphonate esters **9**, (Schemes **33 – 36**)

Scheme **91** illustrates methods for the synthesis of intermediates for the preparation of

10   decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the

preparation of the benzenoid intermediate **91.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **91.1**, the preparation of which is described

in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **91.2**. For

example, the carboxylic acid is first transformed into the benzyl ester, and the product is

15   reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine,

to afford the product **91.2**, in which R is benzyl. This compound is reacted with a brominating

agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product

91.3. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or

carbon tetrachloride, at reflux. The brominated compound **91.3** is then treated with acid, for

20   example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the

tetrahydroisoquinoline **91.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **91.4** can be obtained from 2-hydroxyphenylalanine

91.5, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is

subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem.

25   Rev., 1995, 95, 1797.

Typically, the substrate **91.5** is reacted with aqueous formaldehyde, or an equivalent such as

paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as

described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **91.4**,

in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a

30   platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on

alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-

substituted decahydroisoquinoline **91.6**. The reduction can also be performed
electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **91.4** is subjected to hydrogenation in an alcoholic
solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on

5   alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at
ca 50°, to afford the decahydroisoquinoline **91.6**.

Protection of the carboxyl and NH groups present in **91.6** for example by conversion of the
carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic
Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH

10   into the N-cbz group, as described above, followed by oxidation, using, for example,
pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L.
F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **91.9**, in which R is
trichloroethyl and R_1 is cbz. Reduction of the ketone, for example by the use of sodium
borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl

15   aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol
91.10.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic
solvent such as isopropanol, at ambient temperature, to afford the alcohol **91.10**.

The alcohol **91.6** can be converted into the thiol **91.13** and the amine **91.14**, by means of

20   displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For
example, the alcohol **91.6** can be converted into an activated ester such as the
trifluoromethanesulfonyl ester or the methanesulfonate ester **91.7**, by treatment with
methanesulfonyl chloride and a base. The mesylate **91.7** is then treated with a sulfur
nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or

25   sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement
of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous
ammonia, to afford the thiol **91.13**.

For example, the mesylate **91.7** is reacted with one molar equivalent of sodium thioacetate in a
polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to

30   afford the thioacetate **91.12**, in which R is COCH$_3$. The product then treated with, a mild base
such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as
ethanol, at ambient temperature, to afford the thiol **91.13**.

The mesylate **91.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p399, followed by deprotection as described previously, to afford the amine **91.14**.

5   For example, the mesylate **91.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **91.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J.

10   Org. Chem., 38, 3034, 1973, then yields the amine **91.14**.

The application of the procedures described above for the conversion of the β-carbinol **91.6** to the α-thiol **91.13** and the α-amine **91.14** can also be applied to the α-carbinol **91.10**, so as to afford the β-thiol and β-amine, **91.11**.

15   Scheme **92** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.

In this procedure, an alcohol, thiol or amine **92.1** is reacted with a bromoalkyl phosphonate **92.2**, under the conditions described above for the preparation of the phosphonate **90.4** (Scheme **90**), to afford the displacement product **92.3**. Removal of the ester group, followed

20   by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **92.8**.

For example, the compound **92.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted

25   with a dialkyl 3-bromopropylphosphonate, **92.6**, the preparation of which is described in J. Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product **92.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **92.8**.

Using the above procedures, but employing, in place of the α-thiol **92.5**, the alcohols, thiols or

30   amines **91.6, 91.10, 91.11, 91.13, 91.14**, of either α- or β-orientation, there are obtained the corresponding products **92.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme **93** illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive

5   Organic Transformations, by R. C. Larock, p421.

In this procedure, the amines **91.14** or **91.11** are reacted with a phosphonate aldehyde **93.1**, in the presence of a reducing agent, to afford the alkylated amine **93.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **93.3**.

10   For example, the protected amino compound **91.14** is reacted with a dialkyl formylphosphonate **93.4**, the preparation of which is described in US Patent 3784590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **93.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and

15   N-deprotection, as described herein, (Scheme **96**) then yields the amine **93.6**.

Using the above procedures, but employing, instead of the α-amine **91.14**, the β isomer, **91.11** and/or different aldehydes **93.1**, there are obtained the corresponding products **93.3**, in which the orientation of the side chain is the same as that of the amine precursor.

20   Scheme **94** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate **94.2** is reacted with a mesylate **94.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **94.3**. Deprotection of the ester group, followed by conversion of the acid to the

25   R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **94.4**.

For example, the protected mesylate **94.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **94.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the

30   presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate **94.7**. Deprotection of the ester group, followed by

conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme 96) then yields the amine **94.8**

Using the above procedures, but employing, instead of the phosphonate **94.6**, different phosphonates **94.2**, there are obtained the corresponding products **94.4**.

5

Scheme **95** illustrates the preparation of decahydroisoquinoline phosphonates **95.4** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates **95.1** and a bromomethyl substituted phosphonate **95.2**. The reaction is

10   performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant **95.1**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds **95.3**. Deprotection of the ester group, followed by

15   conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme 96) then yields the amine **95.4**.

For example, the protected alcohol **95.5** is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate **95.6**, the preparation of which is described above, (Scheme **80**). The reaction is conducted in a dipolar aprotic solvent such as, for example,

20   dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **95.6**, to afford the product **95.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **95.8**.

25   Using the above procedures, but employing, instead of the β-carbinol **95.5**, different carbinols, thiols or amines **95.1**, of either α- or β-orientation, and/or different phosphonates **95.2**, in place of the phosphonate **95.6**, there are obtained the corresponding products **95.4** in which the orientation of the side-chain is the same as that of the starting material **95.1**.

30   Schemes **92-95** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme **96** illustrates the conversion of the latter group of compounds **96.1** (in which the group B is link-P(O)(OR^1)$_2$ or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH$_2$) to the corresponding R^{4}R^{5}N amides **96.5**.

As shown in Scheme **96**, the ester compounds **96.1** are deprotected to form the corresponding

5   carboxylic acids **96.2**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R^2, and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **96.2** to the R^{4}R^{5}N amide **96.4** is then accomplished by

10   reaction of the carboxylic acid, or an activated derivative thereof, with the amine R^{4}R^{5}NH **96.3** to afford the amide **96.4**, using the conditions described above for the preparation of the amide **1.6**. Deprotection of the NR^2 group, as described above, then affords the free amine **96.5**.

Scheme 95
Method

95.1 X = O, S, NH
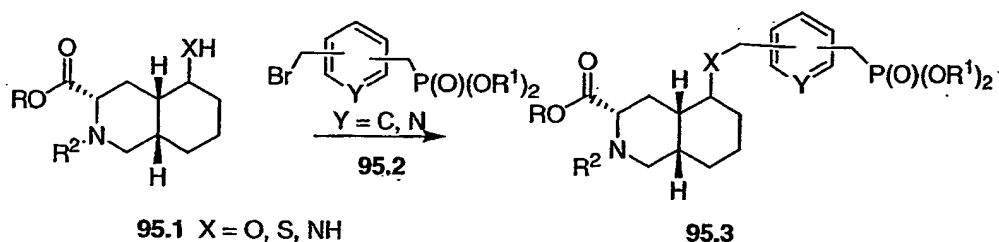
R^2 = protecting group

Example

Scheme 96
Method

96.1
R^2 = protecting group
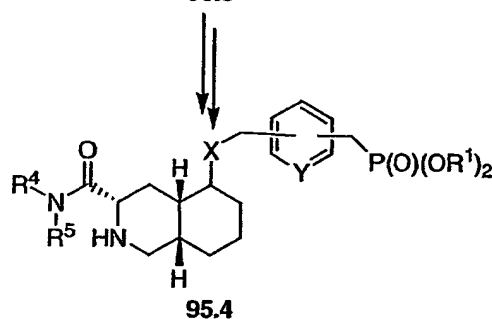
Preparation of the phosphonate-containing tert. butylamides 37.1.

Scheme **97** illustrates the preparation of the amides **37.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters **10** (Schemes **37 – 40**). In

5   this procedure, the BOC-protected decahydroisoquinoline carboxylic acid **97.1** is reacted with the tert. butylamine derivative **25.1**, in which the substituent A is the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], Br, etc, to afford the amide **97.2**. The reaction is conducted as described above for the preparation of the amides **1.3** and **1.6**. The BOC protecting group is then removed to yield the amine **37.1**.
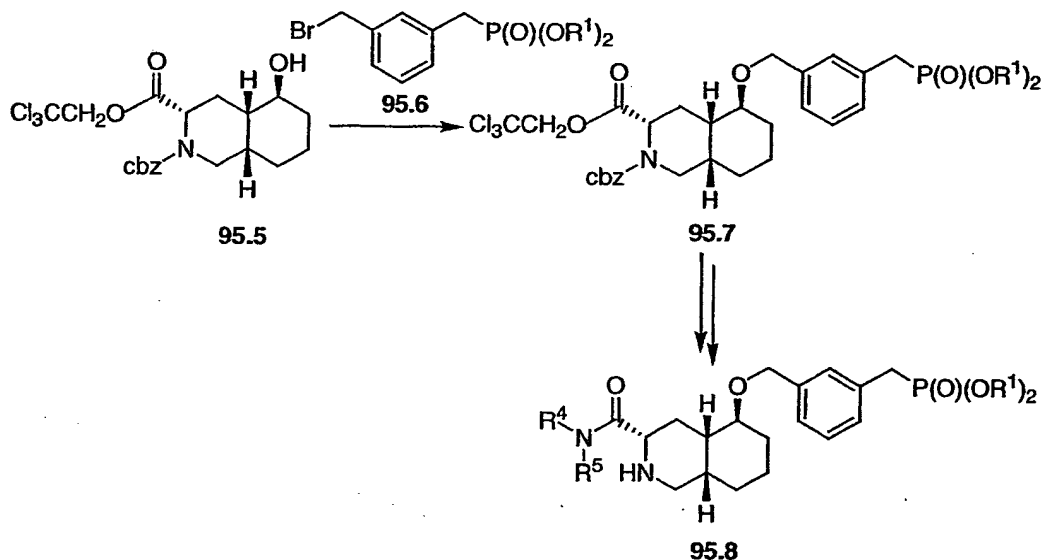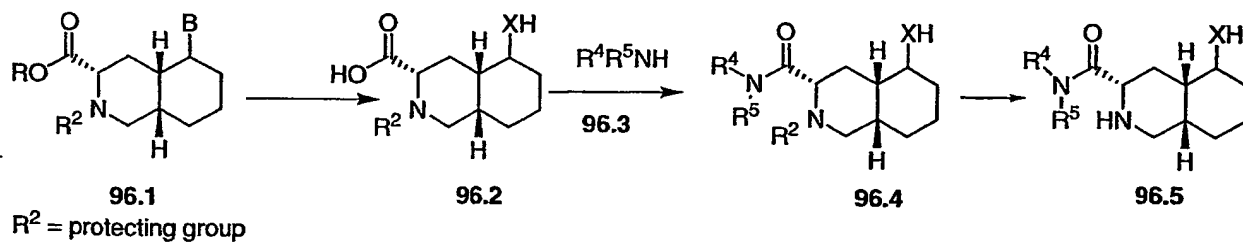
10

Preparation of the phosphonate-containing thiazolidines 21.1.

Schemes **98 - 101** illustrate the preparation of the thiazolidine derivatives **37.1**, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH],

15   Br etc, which are employed in the preparation of the intermediate phosphonate esters **6**. The preparation of the penicillamine analogs **98.5** in which R is alkyl is described in J. Org. Chem., 1986, 51, 5153 and in J. Labelled. Comp. Radiochem., 1987, 24, 1265. The conversion of the penicillamine analogs **98.5** into the corresponding thiazolidines **98.7** is described in J. Med. Chem., 1999, 42, 1789 and in J. Med. Chem., 1989, 32, 466. The above-cited procedures, and

20   their use to afford analogs of the thiazolidines **98.7** are shown in Scheme **98**.
In this procedure, a methyl ketone **98.2** is reacted with methyl isocyanoacetate **98.1** to afford the aminoacrylate product **98.3**. The condensation reaction is conducted in the presence of a base such as butyllithium or sodium hydride, in a solvent such as tetrahydrofuran at from -80° to 0°, to afford after treatment with aqueous ammonium chloride the N-formyl acrylate ester

25   **98.3**. The latter compound is then reacted with phosphorus pentasulfide or Lawessons reagent and the like to yield the thiazoline derivative **98.4**. The reaction is performed in an aprotic solvent such as benzene, for example as described in J. Org. Chem., 1986, 51, 5153. The thiazoline product **98.4** is then treated with dilute acid, for example dilute hydrochloric acid, to produce the aminothiol **98.5**. This compound is reacted with aqueous formaldehyde at pH 5,

30   for example as described in J. Med. Chem., 1999, 42, 1789, to prepare the thiazolidine **98.6**. The product is then converted, as described previously, into the BOC-protected analog **98.7**.

Some examples of the use of the reactions of Scheme **98** for the preparation of functionally substituted thiazolidines **98.7** are shown below.

Scheme **98**, Example **1** illustrates the preparation of the BOC-protected hydroxymethyl thiazolidine **98.11**. In this procedure, methyl isocyanoacetate **98.1** is reacted with

5   hydroxyacetone **98.8** in the presence of a base such as sodium hydride, to yield the aminoacrylate derivative **98.9**. The product is then reacted with phosphorus pentasulfide, as described above, to prepare the thiazoline **98.10**. The latter compound is then converted, as described above, into the thiazolidine derivative **98.11**.

Scheme **98**, Example **2**, depicts the preparation of bromophenyl-substituted thiazolidines

10   **98.14**. In this reaction sequence, methyl isocyanoacetate **98.1** is condensed, as described above, with a bromoacetophenone **98.12** to give the aminocinnamate derivative **98.13**. The latter compound is then transformed, as described above, into the thiazolidine derivative **98.14**.

Scheme **98**, Example **3** depicts the preparation of the BOC-protected

15   thiazolidine-5-carboxylic acid **98.18**. In this procedure, methyl isocyanoacetate **98.1** is reacted, as described above, with trichloroethyl pyruvate **98.15** to afford the aminoacrylate derivative **98.16**. This compound is then transformed, as described above, into the thiazolidine diester **98.17**. The trichloroethyl ester is then cleaved, for example by treatment with zinc in aqueous tetrahydrofuran at pH 4.2, as described in J. Am. Chem. Soc., 88, 852, 1966, to afford the 5-

20   carboxylic acid **98.18**.

Scheme **98**, Example **4**, depicts the preparation of the BOC-protected thiazolidine-4-carboxylic acid incorporating a phosphonate moiety. In this procedure, methyl isocyanoacetate **98.1** is condensed, as described above, with a dialkyl 2-oxopropyl phosphonate **98.19**, (Aldrich); the product **98.20** is then transformed, as described above, into the corresponding

25   4-carbomethoxythiazolidine. Hydrolysis of the methyl ester, for example by the use of one equivalent of lithium hydroxide in aqueous tetrahydrofuran, then yields the carboxylic acid **98.21**.

Scheme **99** illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids

30   incorporating a phosphonate group attached by means of an oxygen atom and an alkylene chain. In this procedure, the hydroxymethyl thiazolidine **98.11** is reacted with a dialkyl bromoalkyl phosphonate **99.1** to afford the ether product **99.2**. The hydroxymethyl substrate

98.11 is treated in dimethylformamide solution with a strong base such as sodium hydride or lithium hexamethyldisilylazide, and an equimolar amount of the bromo compound 99.1 is added. The product 99.2 is then treated with aqueous base, as described above, to effect hydrolysis of the methyl ester to yield the carboxylic acid 99.3.

5   For example, the hydroxymethyl thiazolidine 98.11 is reacted with sodium hydride and a dialkyl bromoethyl phosphonate 99.4 (Aldrich) in dimethylformamide at 70°, to produce the phosphonate product 99.5. Hydrolysis of the methyl ester then affords the carboxylic acid 99.6.

Using the above procedures, but employing, in place of the dialkyl bromoethyl phosphonate 99.4, different bromoalkyl phosphonates 99.1, the corresponding products 99.3 are obtained.

10

Scheme 100 illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of a phenyl group. In this procedure, a bromophenyl-substituted thiazolidine 98.14 is coupled, as described above (Scheme 46) in the presence of a palladium catalyst, with a dialkyl phosphite 100.1, to produce the

15   phenylphosphonate derivative 100.2. The methyl ester is then hydrolyzed to afford the carboxylic acid 100.3.

For example, the BOC-protected 5-(4-bromophenyl)thiazolidine 100.4 is coupled with a dialkyl phosphite 100.1 to yield the product 100.5, which upon hydrolysis affords the

20   carboxylic acid 100.6.

Using the above procedures, but employing, in place of the 4-bromophenyl thiazolidine 100.4, different bromophenyl thiazolidines 98.14, the corresponding products 100.3 are obtained.

Scheme 101 illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of an amide linkage. In this procedure,

25   a thiazolidine-5-carboxylic acid 98.18 is reacted with a dialkyl aminoalkyl phosphonate 101.1 to produce the amide 101.2. The reaction is conducted as described above for the preparation of the amides 1.3 and 1.6. The methyl ester is then hydrolyzed to afford the carboxylic acid 101.3.

For example, the carboxylic acid 98.18 is reacted in tetrahydrofuran solution with an

30   equimolar amount of a dialkyl aminopropyl phosphonate 101.4 (Acros) and dicyclohexylcarbodiimide, to afford the amide 101.5. The methyl ester is then hydrolyzed to afford the carboxylic acid 101.6.

Using the above procedures, but employing, in place of the dialkyl aminopropyl phosphonate **101.4**, different aminoalkyl phosphonates **101.1**, the corresponding products **101.3** are obtained.

Scheme 99
Method
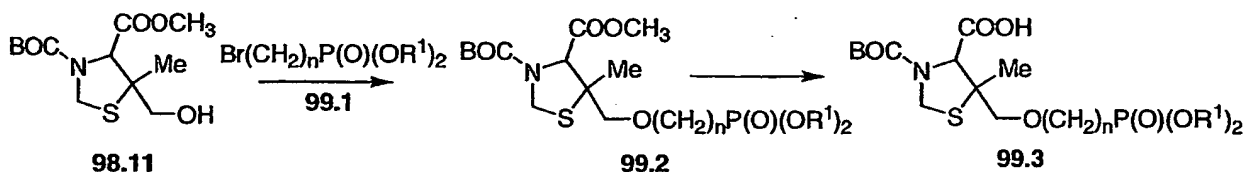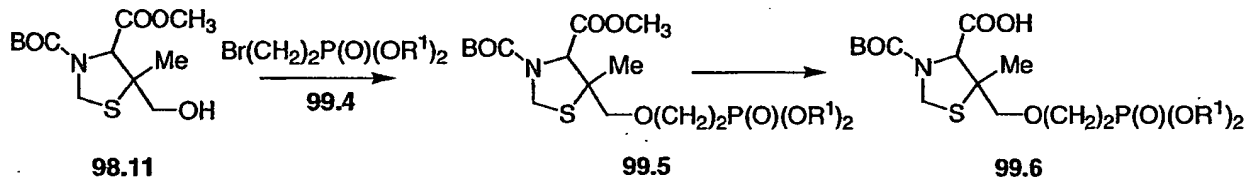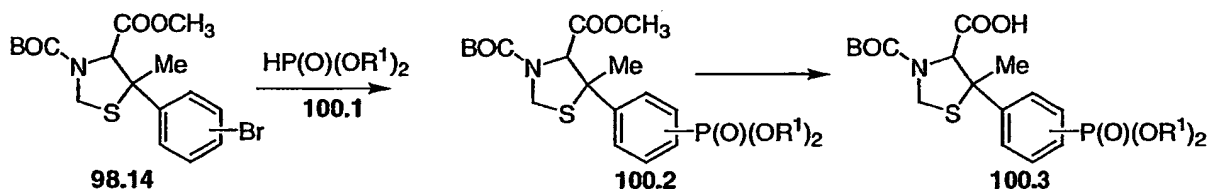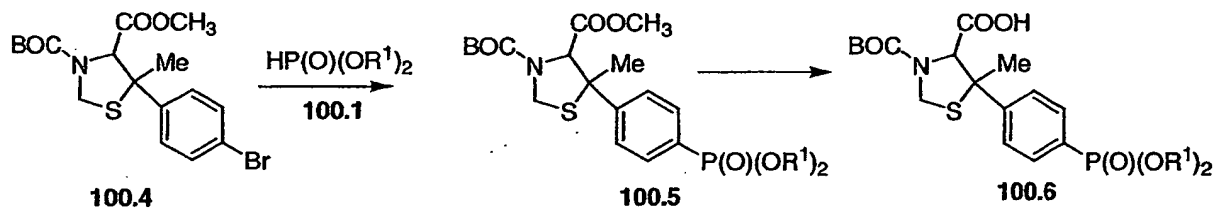
98.11 $Br(CH_2)_nP(O)(OR^1)_2$ 99.1   99.2   99.3

Example

98.11 $Br(CH_2)_2P(O)(OR^1)_2$ 99.4   99.5   99.6

Scheme 100

Method

98.14 $HP(O)(OR^1)_2$ 100.1   100.2   100.3

Example

100.4 $HP(O)(OR^1)_2$ 100.1   100.5   100.6

Scheme 101

Method

98.18 $H_2N(CH_2)_nP(O)(OR^1)_2$ 101.1   101.2   101.3

Example

98.18 $H_2N(CH_2)_3P(O)(OR^1)_2$ 101.4   101.5   101.6

Preparation of carbamates.

5

The phosphonate esters **5 - 12** in which the R⁸CO groups are formally derived from the
carboxylic acids **C38 - C49** (Chart **2c**) contain a carbamate linkage. The preparation of
carbamates is described in Comprehensive Organic Functional Group Transformations, A. R.
Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group
Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **102** illustrates various methods by which the carbamate linkage can be synthesized. As
shown in Scheme **102**, in the general reaction generating carbamates, a carbinol **102.1**, is
converted into the activated derivative **102.2** in which Lv is a leaving group such as halo,
imidazolyl, benztriazolyl and the like, as described herein. The activated derivative **102.2** is
then reacted with an amine **102.3**, to afford the carbamate product **102.4**. Examples **1 – 7** in
Scheme **102** depict methods by which the general reaction can be effected. Examples **8 - 10**
illustrate alternative methods for the preparation of carbamates.

Scheme **102**, Example **1** illustrates the preparation of carbamates employing a chloroformyl
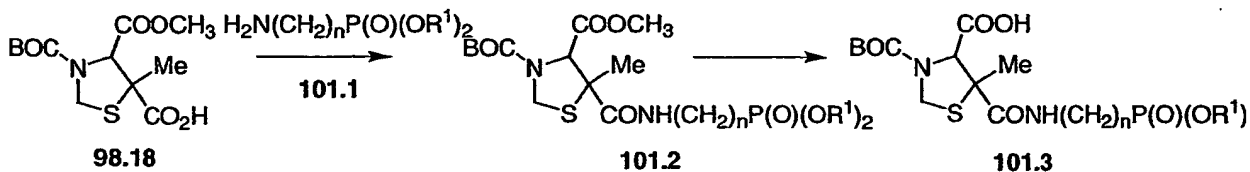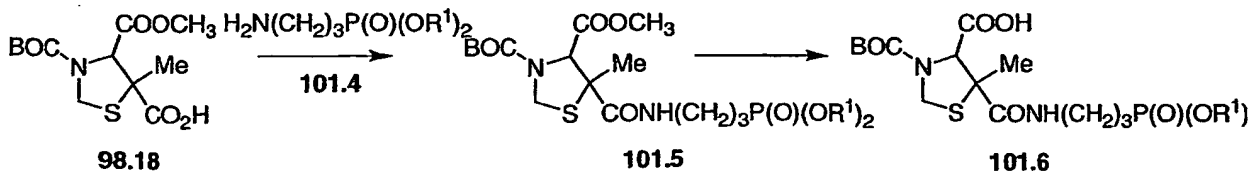derivative of the carbinol **102.5**. In this procedure, the carbinol **102.5** is reacted with
phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol.
3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as
described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **102.6**. The latter
compound is then reacted with the amine component **102.3**, in the presence of an organic or
inorganic base, to afford the carbamate **102.7**. For example, the chloroformyl compound **102.6**
is reacted with the amine **102.3** in a water-miscible solvent such as tetrahydrofuran, in the
presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to
yield the carbamate **102.7**. Alternatively, the reaction is performed in dichloromethane in the
presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **102**, Example **2** depicts the reaction of the chloroformate compound **102.6** with
imidazole to produce the imidazolide **102.8**. The imidazolide product is then reacted with the
amine **102.3** to yield the carbamate **102.7**. The preparation of the imidazolide is performed in
an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is
conducted in a similar solvent at ambient temperature, optionally in the presence of a base
such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

- 1113 -

Scheme 102 Example 3, depicts the reaction of the chloroformate **102.6** with an activated
hydroxyl compound R"OH, to yield the mixed carbonate ester **102.10**. The reaction is
conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a
base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected

5   from the group of compounds **102.19** - **102.24** shown in Scheme **102**, and similar compounds.
For example, if the component R"OH is hydroxybenztriazole **102.19**, N-hydroxysuccinimide
102.20, or pentachlorophenol, **102.21**, the mixed carbonate **102.10** is obtained by the reaction
of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of
dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which

10   the component R"OH is pentafluorophenol **102.22** or 2-hydroxypyridine **102.23** can be
performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986,
303, and Chem. Ber. 118, 468, 1985.

Scheme **102** Example **4** illustrates the preparation of carbamates in which an
alkyloxycarbonylimidazole **102.8** is employed. In this procedure, a carbinol **102.5** is reacted

15   with an equimolar amount of carbonyl diimidazole **102.11** to prepare the intermediate **102.8**.
The reaction is conducted in an aprotic organic solvent such as dichloromethane or
tetrahydrofuran. The acyloxyimidazole **102.8** is then reacted with an equimolar amount of the
amine R'NH$_2$ to afford the carbamate **102.7**. The reaction is performed in an aprotic organic
solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the

20   carbamate **102.7**.

Scheme **102**, Example **5** illustrates the preparation of carbamates by means of an intermediate
alkoxycarbonylbenztriazole **102.13**. In this procedure, a carbinol ROH is reacted at ambient
temperature with an equimolar amount of benztriazole carbonyl chloride **102.12**, to afford the
alkoxycarbonyl product **102.13**. The reaction is performed in an organic solvent such as

25   benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as
described in Syn., 1977, 704. The product is then reacted with the amine R'NH$_2$ to afford the
carbamate **102.7**. The reaction is conducted in toluene or ethanol, at from ambient
temperature to about 80° as described in Syn., 1977, 704.

Scheme **102**, Example **6** illustrates the preparation of carbamates in which a carbonate

30   (R"O)$_2$CO, **102.14**, is reacted with a carbinol **102.5** to afford the intermediate
alkyloxycarbonyl intermediate **102.15**. The latter reagent is then reacted with the amine R'NH$_2$
to afford the carbamate **102.7**. The procedure in which the reagent **102.15** is derived from

hydroxybenztriazole **102.19** is described in Synthesis, 1993, 908; the procedure in which the

reagent **102.15** is derived from N-hydroxysuccinimide **102.20** is described in Tet. Lett., 1992,

2781; the procedure in which the reagent **102.15** is derived from 2-hydroxypyridine **102.23** is

described in Tet. Lett., 1991, 4251; the procedure in which the reagent **102.15** is derived from

5   4-nitrophenol **102.24** is described in Syn. 1993, 103. The reaction between equimolar amounts

of the carbinol ROH and the carbonate **102.14** is conducted in an inert organic solvent at

ambient temperature.

Scheme **102**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides

102.16. In this procedure, an alkyl chloroformate **102.6** is reacted with an azide, for example

10   sodium azide, to afford the alkoxycarbonyl azide **102.16**. The latter compound is then reacted

with an equimolar amount of the amine R'NH$_2$ to afford the carbamate **102.7**. The reaction is

conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for

example as described in Syn., 1982, 404.

Scheme **102**, Example **8** illustrates the preparation of carbamates by means of the reaction

15   between a carbinol ROH and the chloroformyl derivative of an amine **102.17**. In this

procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook,

Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent

such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate

102.7.

20   Scheme **102**, Example **9** illustrates the preparation of carbamates by means of the reaction

between a carbinol ROH and an isocyanate **102.18**. In this procedure, which is described in

Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants

are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane

and the like, to afford the carbamate **102.7**.

25   Scheme **102**, Example **10** illustrates the preparation of carbamates by means of the reaction

between a carbinol ROH and an amine R'NH$_2$. In this procedure, which is described in Chem.

Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic

solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and

selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford

30   the carbamate **102.7**.

Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1** - **102** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may

5   be the same or different. The R^1 groups attached to a phosphonate esters **1** - **12**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **103**. The group R in Scheme **103** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1** - **12** or in precursors thereto. The R^1 group may be changed, using

10   the procedures described below, either in the precursor compounds, or in the esters **1** - **12**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **103.1** into the corresponding phosphonate monoester

15   **103.2** (Scheme **103**, Reaction 1) can be accomplished by a number of methods. For example, the ester **103.1** in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound **103.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about

20   110°. The conversion of the diester **103.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **103.2** can be effected by treatment of the ester **103.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **103.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **103.2** in which R^1

25   is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **103.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described

30   in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **103.1** or a phosphonate monoester **103.2** into the corresponding phosphonic acid **103.3** (Scheme 103, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for

5   example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **103.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **103.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **103.2** in which R^1 is alkenyl

10   such as, for example, allyl, can be converted into the phosphonic acid **103.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **103.1** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of

15   phosphonate esters **103.1** in which R^1 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **103.2** into a phosphonate diester **103.1** (Scheme 103, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **103.2** is

20   reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the

25   reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **103.2** to the diester **103.1** can be effected by the use of the Mitsonobu reaction, as described above

30   (Scheme 47). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **103.2** can be transformed into the phosphonate diester **103.1**, in
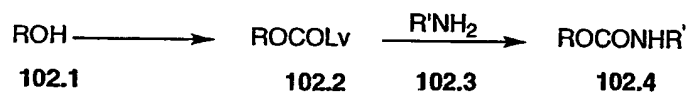
which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the

5   phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **103.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as

10   triethylamine, to afford the phosphonate diester **103.1**.

A phosphonic acid $R\text{-link-}P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **103**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-}P(O)(OR^1)_2$ **103.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.
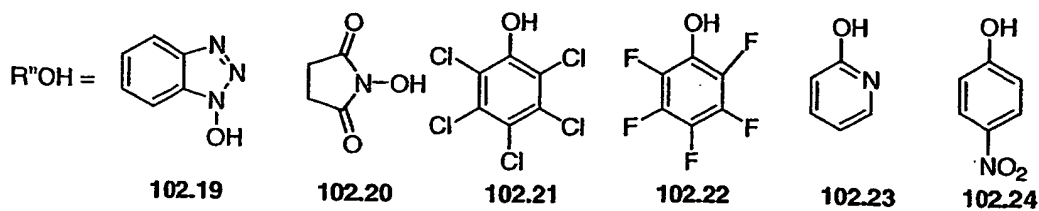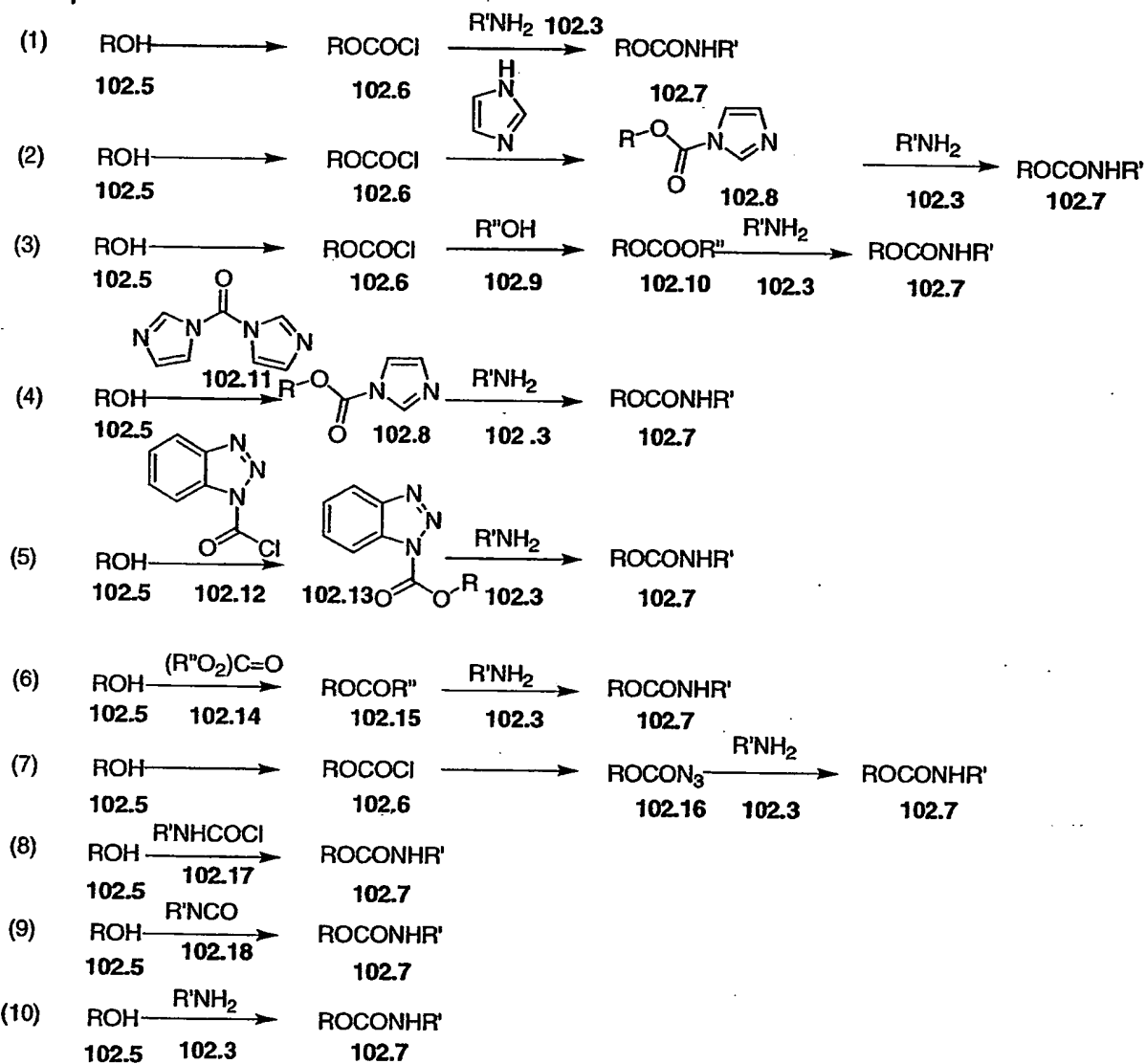
15   A phosphonic acid $R\text{-link-}P(O)(OH)_2$ **103.3** can be transformed into a phosphonate diester $R\text{-link-}P(O)(OR^1)_2$ **103.1** (Scheme **103**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **103.3** can be transformed into phosphonic esters **103.1** in

20   which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **103.3** can be transformed into phosphonic esters **103.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as

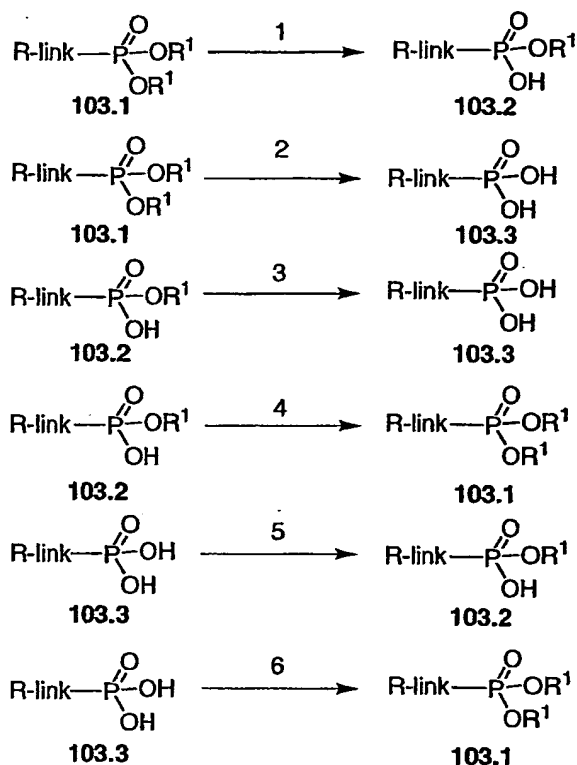25   cesium carbonate, to afford the phosphonic ester **103.1**.

Scheme 102

General reaction

$$ROH \longrightarrow ROCOLv \xrightarrow{R'NH_2} ROCONHR'$$

102.1   102.2   102.3   102.4

Examples

(1) $ROH \longrightarrow ROCOCl \xrightarrow{R'NH_2 \ 102.3} ROCONHR'$

102.5   102.6   102.7

(2) $ROH \longrightarrow ROCOCl \longrightarrow$ $\xrightarrow{R'NH_2} ROCONHR'$

102.5   102.6   102.8   102.3   102.7

(3) $ROH \longrightarrow ROCOCl \xrightarrow{R''OH} ROCOOR'' \xrightarrow{R'NH_2} ROCONHR'$

102.5   102.6   102.9   102.10   102.3   102.7

(4) $ROH \xrightarrow{102.11} $ $\xrightarrow{R'NH_2} ROCONHR'$

102.5   102.8   102.3   102.7

(5) $ROH \xrightarrow{102.12} $ $\xrightarrow{R'NH_2} ROCONHR'$

102.5   102.13   102.3   102.7

(6) $ROH \xrightarrow{(R''O_2)C=O} ROCOR'' \xrightarrow{R'NH_2} ROCONHR'$

102.5   102.14   102.15   102.3   102.7

(7) $ROH \longrightarrow ROCOCl \longrightarrow ROCON_3 \xrightarrow{R'NH_2} ROCONHR'$

102.5   102.6   102.16   102.3   102.7

(8) $ROH \xrightarrow[102.17]{R'NHCOCl} ROCONHR'$

102.5   102.7

(9) $ROH \xrightarrow[102.18]{R'NCO} ROCONHR'$

102.5   102.7

(10) $ROH \xrightarrow[102.3]{R'NH_2} ROCONHR'$

102.5   102.7

$R''OH =$

102.19   102.20   102.21   102.22   102.23   102.24

Scheme 103

R-link—$\overset{O}{\underset{OR^1}{\overset{\|}{P}}}$—OR^1 $\xrightarrow{\ 1\ }$ R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OR^1

103.1   **103.2**

R-link—$\overset{O}{\underset{OR^1}{\overset{\|}{P}}}$—OR^1 $\xrightarrow{\ 2\ }$ R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OH

103.1   **103.3**

R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OR^1 $\xrightarrow{\ 3\ }$ R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OH

103.2   **103.3**

R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OR^1 $\xrightarrow{\ 4\ }$ R-link—$\overset{O}{\underset{OR^1}{\overset{\|}{P}}}$—OR^1

103.2   **103.1**

R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OH $\xrightarrow{\ 5\ }$ R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OR^1

103.3   **103.2**

R-link—$\overset{O}{\underset{OH}{\overset{\|}{P}}}$—OH $\xrightarrow{\ 6\ }$ R-link—$\overset{O}{\underset{OR^1}{\overset{\|}{P}}}$—OR^1

103.3   **103.1**

General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties (Schemes **45** - **101**) are, with appropriate modifications known to one skilled in the art, transferable to

5   different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into hydroxymethyl benzoic acids (Schemes **45 - 52**) are applicable to the introduction of phosphonate moieties into the dimethoxyphenol, quinoline, phenylalanine, thiophenol, tert. butylamine, benzylamine, decahydroisoquinoline or thiazolidine substrates, and the methods described herein for the introduction of phosphonate moieties into the

10   dimethoxyphenol, quinoline, phenylalanine, thiophenol, tert. butylamine, benzylamine, decahydroisoquinoline or thiazolidine substrates, (Schemes **53 - 101**) are applicable to the introduction of phosphonate moieties into carbinol substrates.

Preparation of phosphonate intermediates 11 and 12 with phosphonate moieties

15   incorporated into the groups R^{8}CO and R^{10}R^{11}N.

The chemical transformations described in Schemes **1 - 103** illustrate the preparation of compounds **1 -10** in which the phosphonate ester moiety is attached to the benzoic acid moiety, (Schemes **46 - 52**), the dimethylphenol moiety (Schemes **53 - 56**), the quinoline

5   carboxamide moiety (Schemes **57 - 61**), the 5-hydroxyisoquinoline moiety (Schemes **62 - 66**), the phenylalanine moiety (Schemes **67 - 71**), the thiophenol moiety, (Schemes **72 - 83**), the tert. butylamine moiety, (Schemes **84 - 87**), the benzylamine moiety, (Schemes **88 - 90**), the decahydroisoquinoline moiety, (Schemes **91 - 97**) or the thiazolidine moiety, (Schemes **98 - 101**). The various chemical methods employed for the preparation of phosphonate groups can,

10   with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^8COOH and $R^{10}R^{11}NH$, as defined in Charts **3a, 3b, 3c** and **4**. The resultant phosphonate-containing analogs, designated as $R^{8a}COOH$ and $R^{10a}R^{11a}NH$ can then, using the procedures described above, be employed in the preparation of the compounds **11** and **12**. The procedures required for the utilization of the

15   phosphonate-containing analogs $R^{8a}COOH$ and $R^{10a}R^{11a}NH$ are the same as those described above for the utilization of the R^8COOH and $R^{10}R^{11}NH$ reactants.

Cyclic carbonyl phosphonate protease inhibitors (CCPPI)

20   **Scheme Section B**

Schemes 1 and 2 are described below in the Examples.

Scheme 1

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Scheme 2

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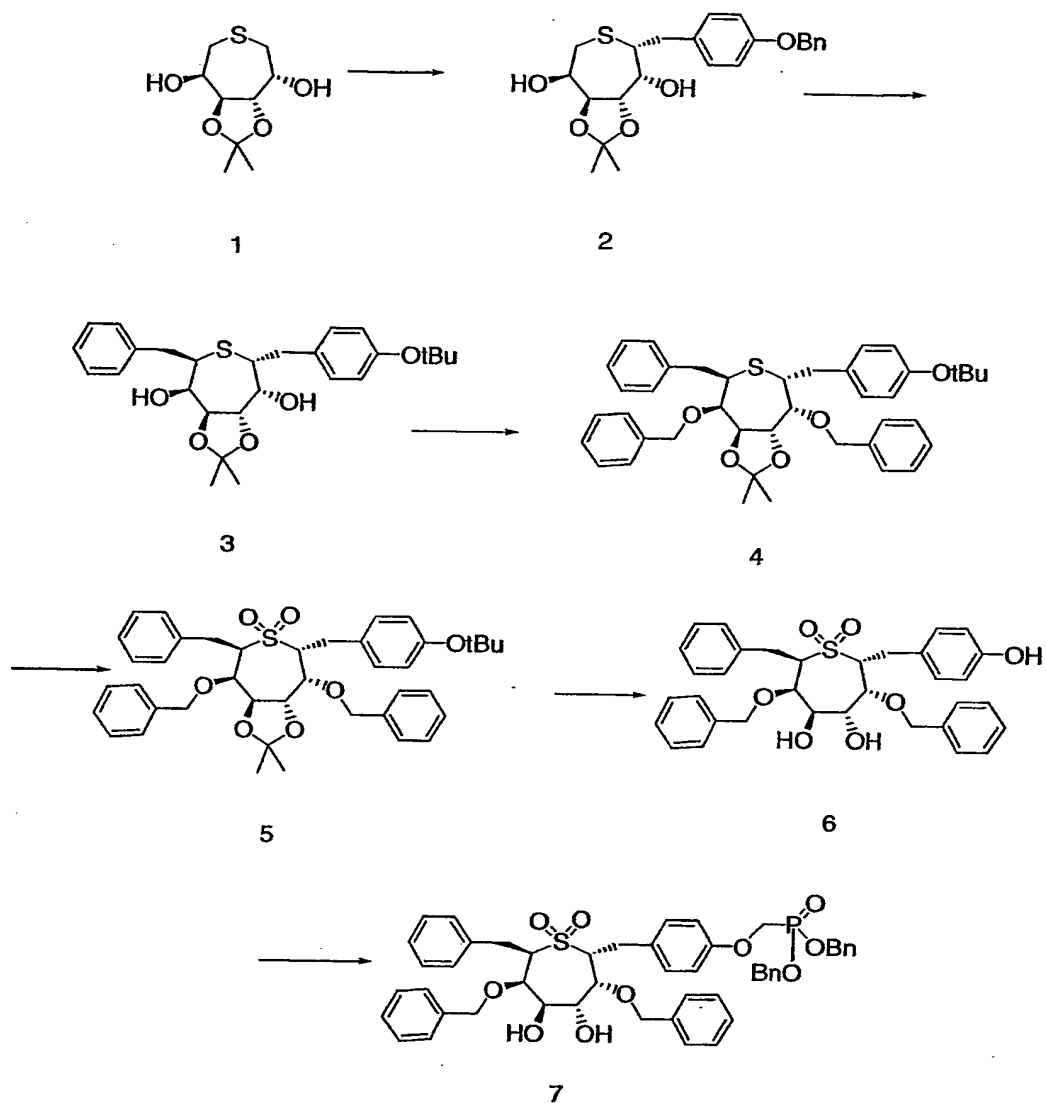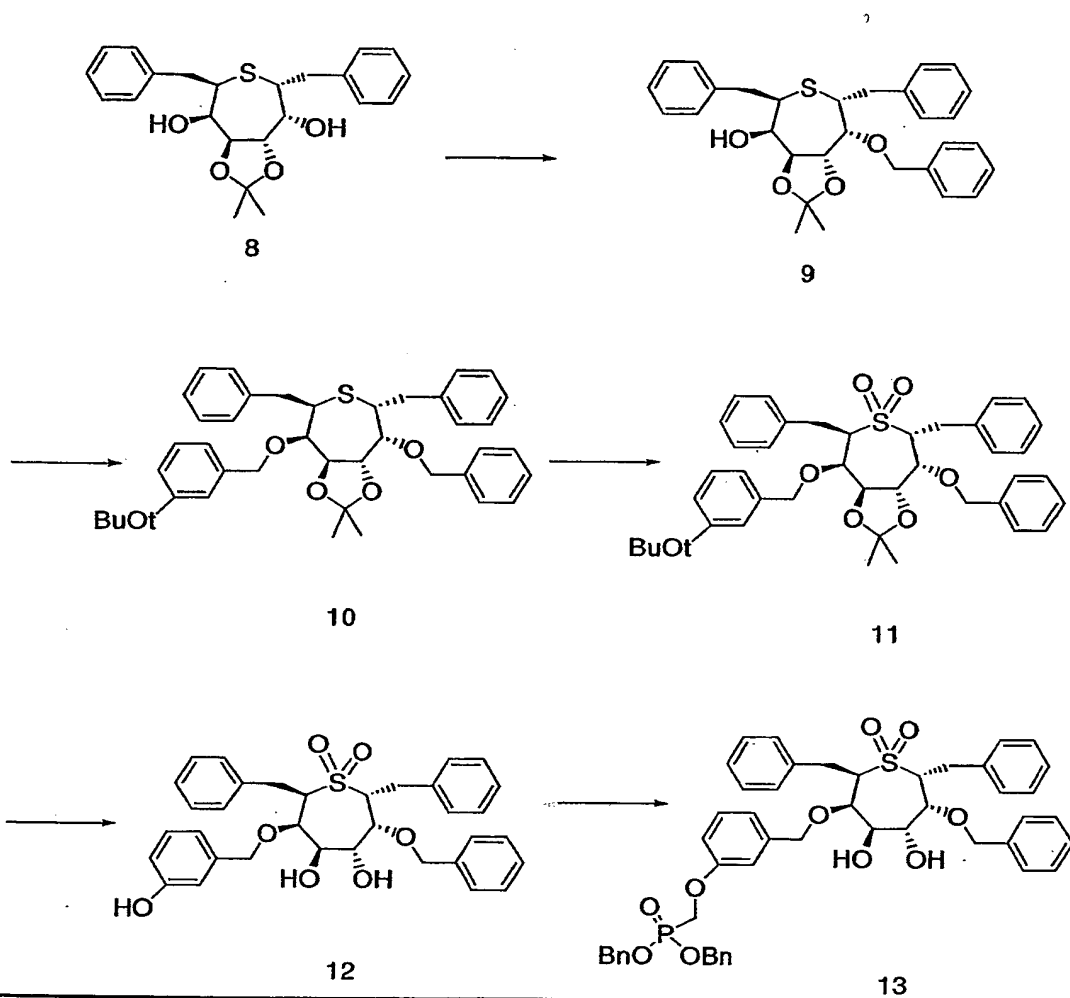
Example Section B

Example 1

Scheme 1 : Example, [4-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-2-
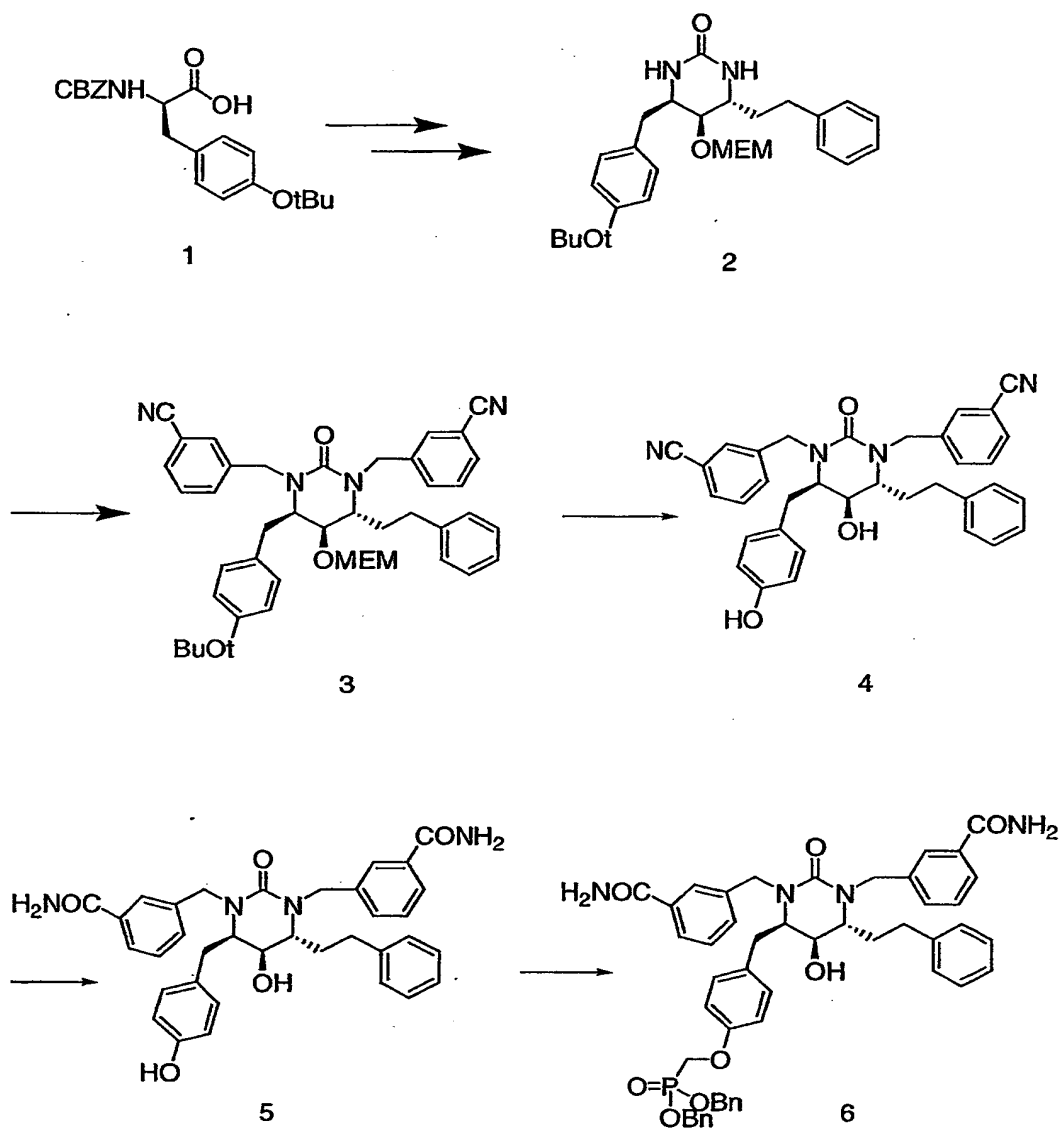5   ylmethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester (7)

The cyclic sulfide **1** is prepared according to the procedures reported by Kim et al. (J. Med.
Chem. 1996, 39, 3431-3434) and Bischofberger (WO96/14314, Gilead Sciences). Treatment
of the sulfide **1** with 4-benzyloxybenzaldehyde affords the benzyl ether **2** (J. Med. Chem.
10   1996, 39, 3431-3434). A second alkylation with benzaldehyde gives **3** which is subsequently
treated with excess benzylbromide to afford the full substituted product **4**. Ozone is used to
covert the sulfide to the sulfone **5** (J. Med. Chem. 1996, 39, 3431-3434). Sulfone **5** is treated
with TFA to give the phenol **6** which upon alkyaltion with trifluoro-methanesulfonic acid bis-
benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) gives the
15   dibenzyl phosphonate **7**.

The meta analog, [3-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-2-
ylmethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester and ortho analog, [2-(7-Benzyl-3,6-
bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-2-ylmethyl)-phenoxymethyl]-phosphonic
20   acid dibenzyl ester are prepared using Scheme 1 except 4-benzyloxybenzaldehyde is replaced
with 3-benzyloxybenzaldehyde and 2-benzyloxybenzaldehyde respectively.

Example 2

Scheme 2 : Example, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-3-
25   yloxymethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester (13).

The sulfide **8** is prepared according to the procedure of Kim et al. (J. Med. Chem.
1996, 39, 3431-3434) and is then treated with benzyl bromide in the presence of sodium
hydride to give the benzyl ether **9**. A second treatment with 3-t-butyloxybenzylchloride in the
30   presence of sodium hydride affords the benzyl ether **10**. Ozone treatment of the benzyl ether
10 gives the sulfone **11**.(J. Med. Chem. 1996, 39, 3431-3434) which is then treated with TFA
to give the phenol **12** (Green). Phenol **12** is treated with trifluoro-methanesulfonic acid bis-

benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to give the dibenzyl phosphonate **13**.

The para analog, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-3-yloxymethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester, and ortho analog, [3-(2,7-

5   Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-3-yloxymethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester, are prepared using the same procedures found in Scheme 2 except utilizing the 4-t-butyloxybenzylchloride and 2-t-butyloxybenzylchloride instead of 3-t-butyloxybenzylchloride. The benzylchlorides are prepared from the corresponding commercially available benzylalcohols by treatment with thionyl chloride (*Jour. Chem. Soc.*

10   (1956), 2455-2461).

Scheme Section C

Schemes 1-4 are described in the Examples.

Scheme 1

Scheme 2

Scheme 3

7 → 14

15 → 16

17 → 18

19 → 20

Scheme 3

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22

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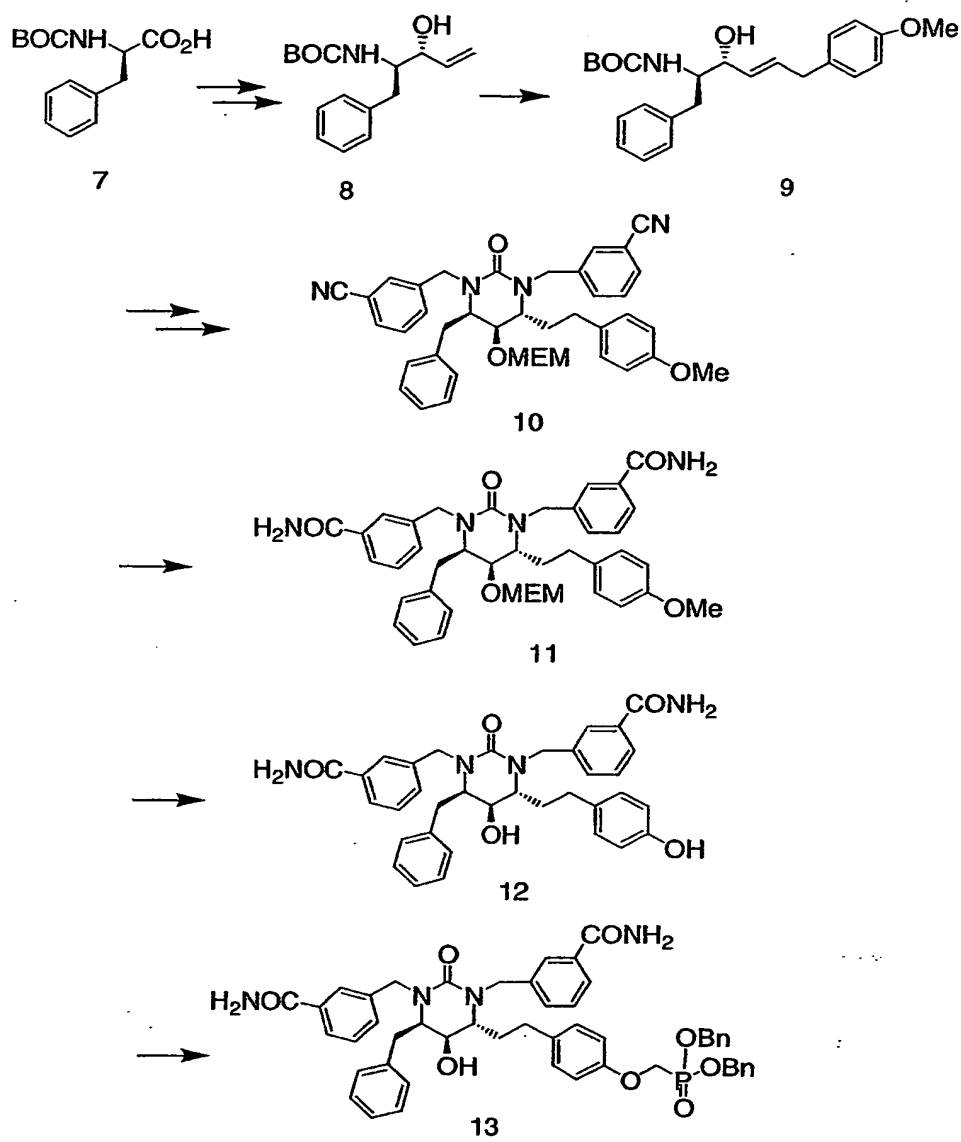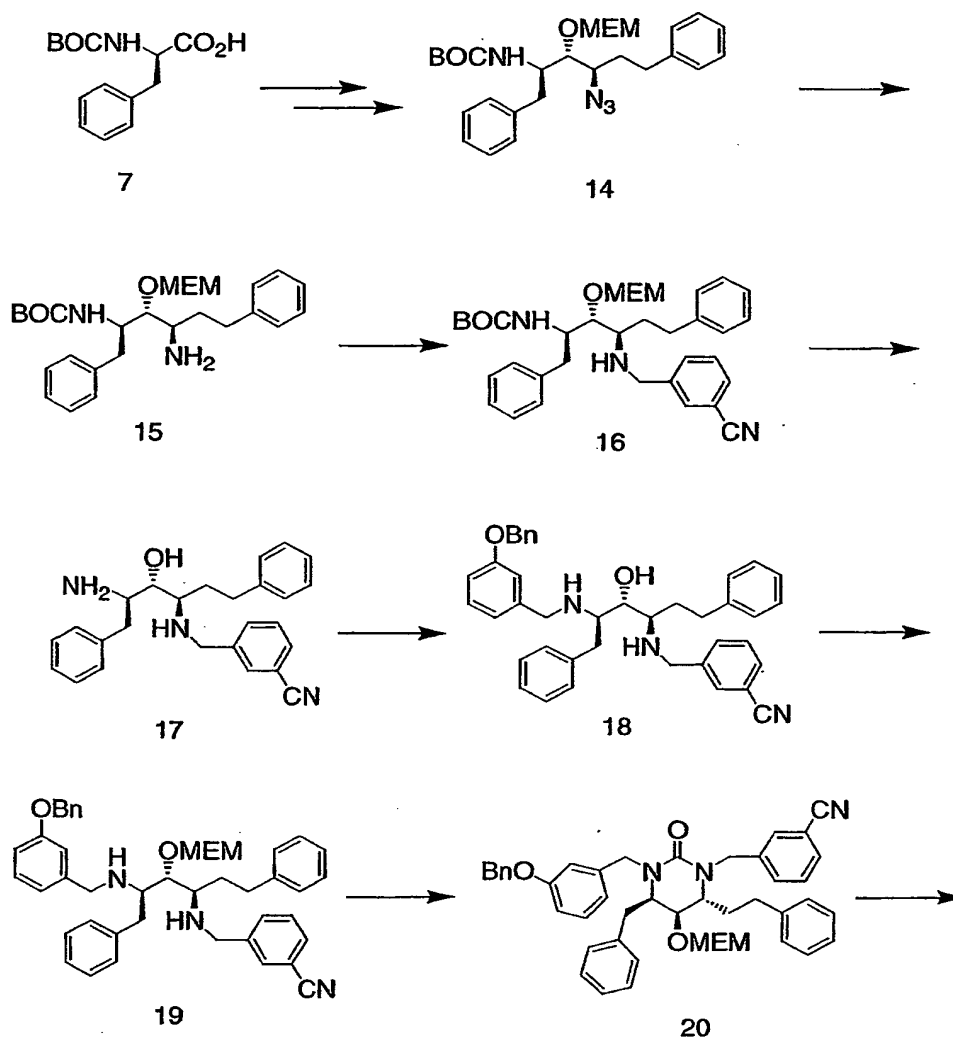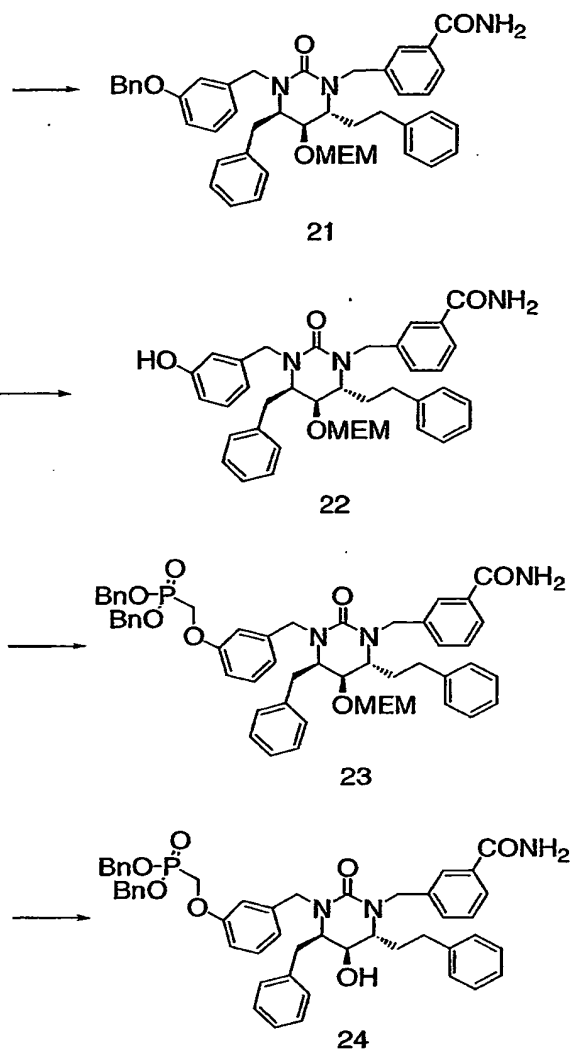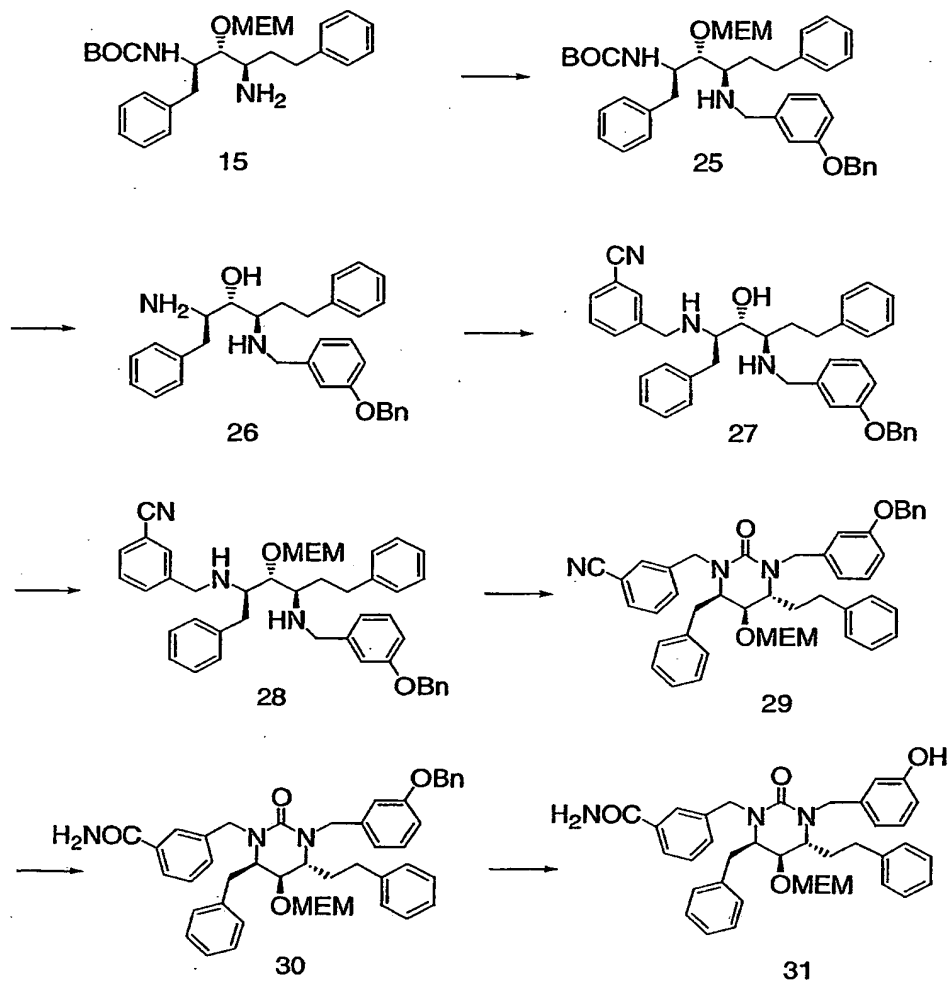
Scheme 4

Scheme 4 (continued)
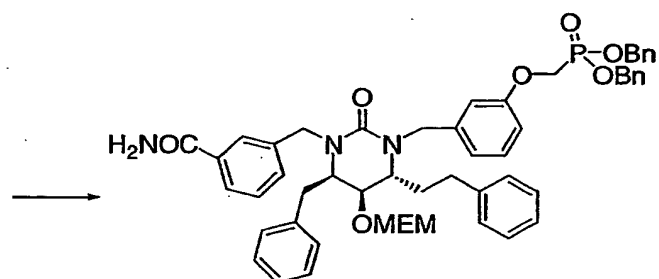
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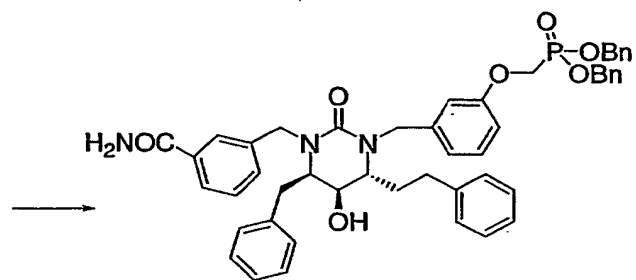
33

Example Section C

Example 1

Scheme 1 : Example, {4-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-

5   hexahydro-pyrimidin-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (6)

Commercially available Z-D-Tyr(TBU)-OH 1 is converted to the tetrahydropyrimidine

2 using the same procedures reported by De Lucca for conversion of Z-Phe into the analogous

tetrahydropyrimidinone (J. Med. Chem. 1997, 40, 1707-1719). Bis-alkylation by treatment

with excess m-cyanobenzylbromide affords the disubstituted urea 3 (J. Med. Chem. 1997, 40,

10   1707-1719). Removal of the MEM group and the t-butyl ether using standard conditions e.g.

TFA (Green) affords the diol 4. Treatment of the diol 4 with hydrogen peroxide in DMSO

affords the carboxamide 5. Alkyation of 5 with trifluoro-methanesulfonic acid bis-benzyloxy-

phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) affords the dibenzyl

phosphonate 6.

15   The meta analog, {3-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-

hexahydro-pyrimidin-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para

analog, {2-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-

4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using Scheme 1

except substituting Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH for Z-D-Tyr(TBU)-OH

20   respectively. The Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH amino acids are prepared

from the unprotecetd amino acids. Thus, D-m-Tyr-OH and D-o-Tyr-OH (see Abbott scheme

1) are treated with dibenzyl dicarbonate in the presence of base e.g. triethylamine to afford the

Z-D-m-Tyr-OH and Z-D-o-Tyr-OH protected amino acids respectively. Further treatment of

Z-D-m-Tyr-OH and Z-D-o-Tyr-OH with t-butyl chloride in the presence of base e.g. pyridine

25   affords the Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH amino acids respectively

(Green).

Example 2

Scheme 2 : Example, (4-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-

30   ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxymethyl)-phosphonic acid

dibenzyl ester (13)

Boc-Phe 7 is converted to the allylic alcohol 8 using the same procedures reported by De

Lucca et al. for the conversion of Z-Phe to the corresponding Z- allylic alcohol (J. Med.

Chem. 1997, 40, 1707-1719). The allylic alcohol 8 is reacted with 4-

methoxybenzylmagnesium chloride to afford the alkene 9 (J. Med. Chem. 1997, 40, 1707-

5   1719). The 4-methoxybenzylmagnesium chloride is prepared from 4-methoxybenzylchloride

according to the procedure of Van Campen et al. (J. Amer. Chem. Soc. 1948, 70 p2296).

The alkene 9 is converted to the tetrahydropyrimidinone 10 using the same series of

procedures reported by De Lucca et al. (J. Med. Chem. 1997, 40, 1707-1719). Treatment of

the nitrile 10 with hydrogen peroxide in DMSO affords the carboxamide 11 (Synthesis, 1989,

10   949-950). The carboxamide 11 is treated with trimethylsilylbromide to form the phenol 12

(Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-

phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to yield the dibenzyl

phosphonate 13.

15   The ortho, (2-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-

oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxymethyl)-phosphonic acid dibenzyl ester and

meta, (3-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-

hexahydro-pyrimidin-4-yl]-ethyl}-phenoxymethyl)-phosphonic acid dibenzyl ester analogs, are

prepared using the same procedures reported in Scheme 2 except 4-methoxybenzylmagnesium

20   chloride is replaced with 2-methoxybenzylmagnesium chloride and 3-

methoxybenzylmagnesium chloride respectively. The grignard reagents are prepared from

commercially available benzyl chlorides using the procedure of Van Campen et al. (J. Amer.

Chem. Soc. 1948, 70 p2296).

25   Example 3

Scheme 3 : Example, {3-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-

tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (24).

Boc-Phe 7 is converted into the azide 14 using the same procedures reported by De Lucca et

30   al. for the conversion of CBZ-Phe into the analogous CBZ azide (J. Med. Chem. 1997, 40,

1707-1719). Catalytic hydrogenolysis of the azide affords the amine 15 (J. Med. Chem. 1997,

40, 1707-1719). Reductive amination of the amine with 3-cyanobenzaldehyde (US 6313110)

affords the secondary amine 16. Treatment with 4N HCl affords the primary amine 17 (Green). Reductive amination with 3-benzyloxybenzadehyde affords the benzyl ether 18 (US 6313110). Treatment of the benzyl ether 18 with MEM-chloride in the presence of base (e.g. DIEA) forms the MEM protected product 19 (J. Med. Chem. 1997, 40, 1707-1719).

5   Treatment of diamine 19 with CDI affords the tetrahydropyrimidinone 20. Treatment of the nitrile 20 with DMSO and hydrogen peroxide (Synthesis 1989, 949-950) affords the carboxamide 21. Catalytic hydrogenolysis affords the phenol 22 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 23. Removal of

10   the MEM group using trifluoroacetic acid affords the product 24 (Green).

The ortho {2-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester. and para, {4-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-

15   ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using the same procedures reported in Scheme 3 except substituting 3-benzyloxybenzaldehyde with 2-benzyloxybenzaldehyde and 4-benzyloxybenzaldehyde respectively.

Example 4

20   Scheme 4 : Example, {3-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (33)

        The amine 15 (Scheme 3) is transformed to the secondary amine 25 through reductive amination with 3-benzyloxybenzadehyde (US 6313110). Treatment of BOC-amine 25 with

25   trifluoroacetic acid releases the primary amine 26 (Green) which is then subjected to a second reductive amination with 3-cyanobenzaldehyde to afford the bis-substituted amine 27 (US 6313110). Treatment of the benzyl ether 27 with MEM-chloride in the presence of base (e.g. DIEA) forms the MEM protected product 28 (J. Med. Chem. 1997, 40, 1707-1719). Treatment of diamine 28 with CDI affords the tetrahydropyrimidinone 29. Treatment of the

30   nitrile 29 with DMSO and hydrogen peroxide (Synthesis 1989, 949-950) affords the carboxamide 30. Catalytic hydrogenolysis affords the phenol 31 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the

presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 32. Removal of
the MEM group using trifluoroacetic acid affords the product 33 (Green).
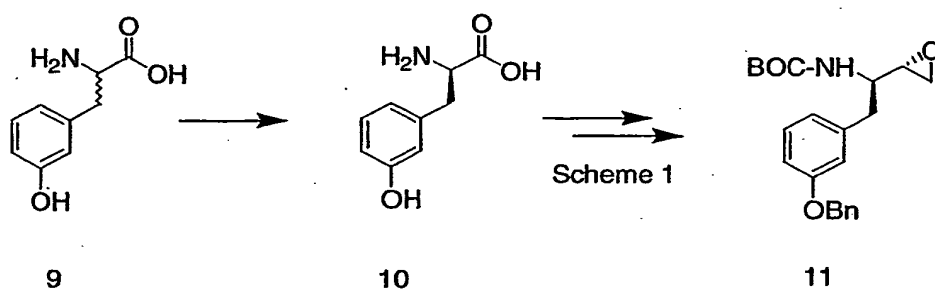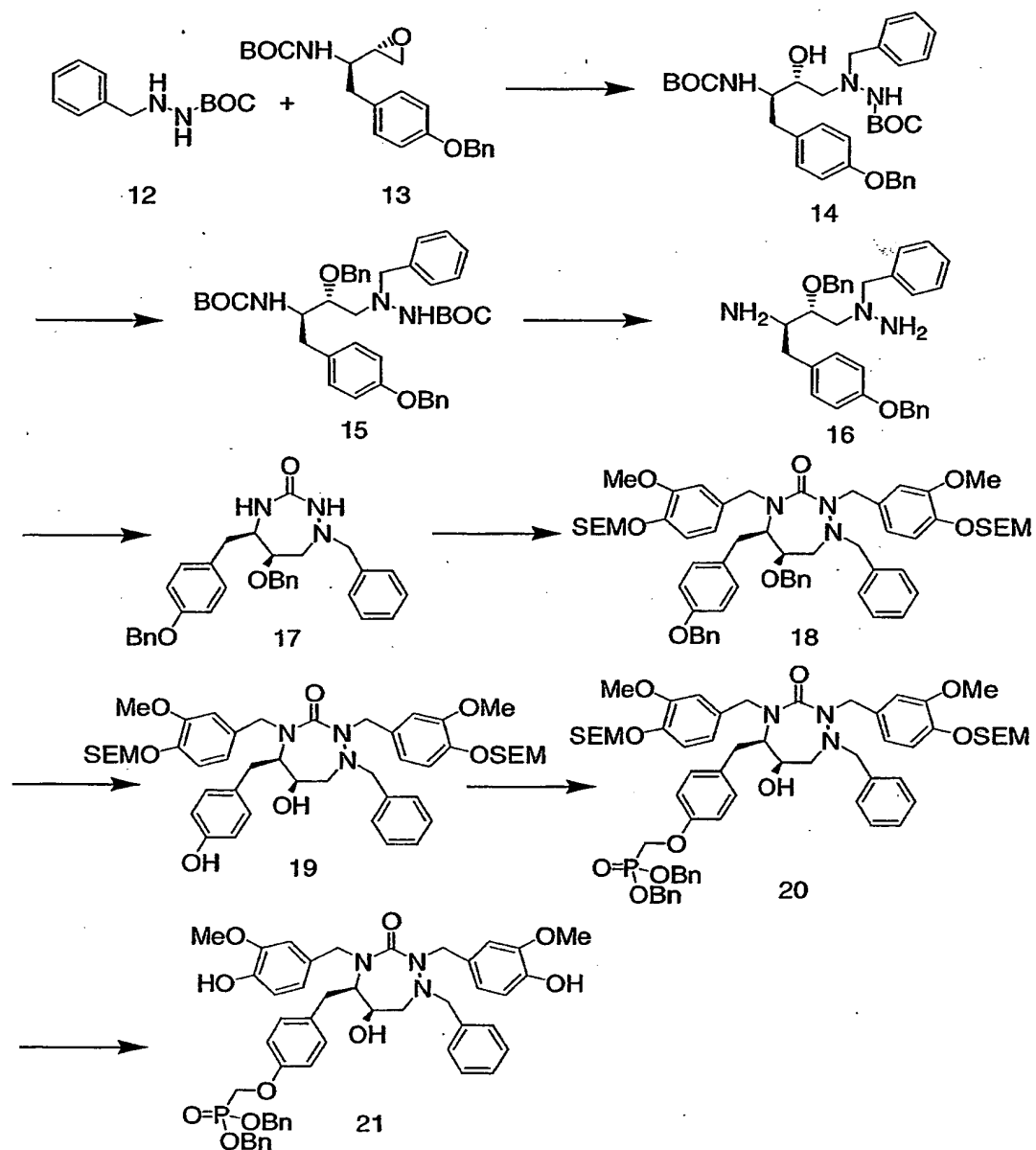
Example 5

5   Ortho analog, {2-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-
pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog, {4-[4-
Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-
ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using Scheme 4 except
replacing 3-benzyloxybenzadehyde with 2- benzyloxybenzadehyde and 4-

10 benzyloxybenzadehydes respectively.

Scheme Section D

Schemes 1-6 are described in the examples.

Scheme 1

Scheme 2

9   10   11
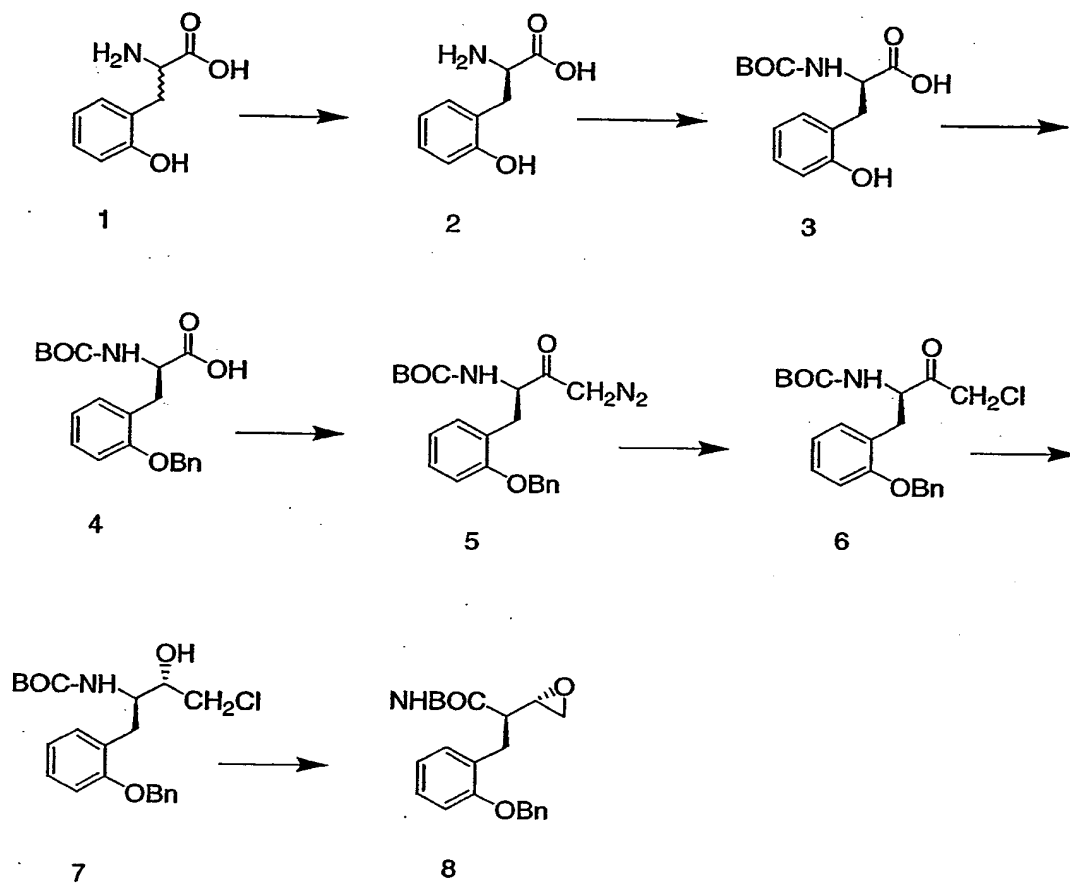
Scheme 1

Scheme 3

Scheme 4

Scheme 5

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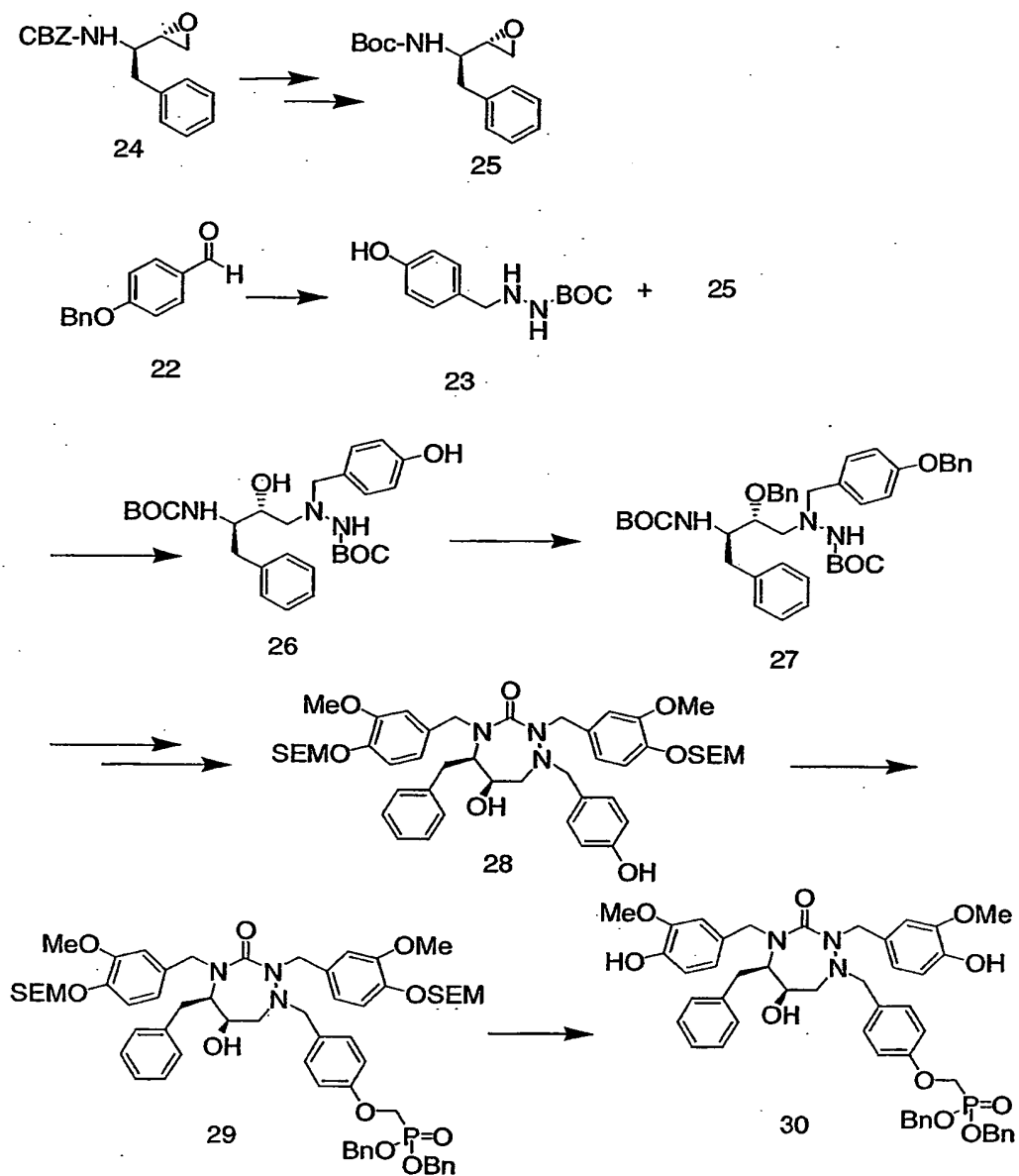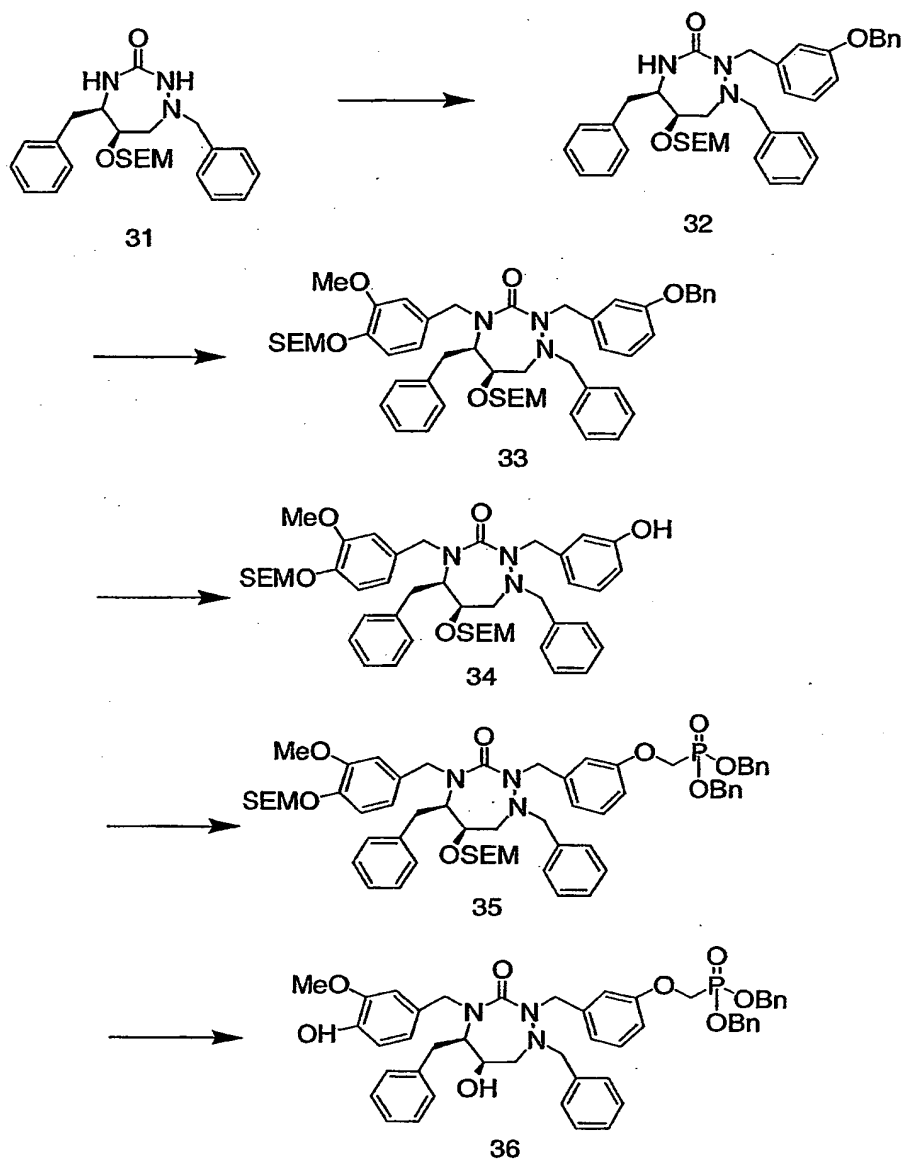
Scheme 6

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Example Section D

Example 1

Scheme 1 : Example; [2-(2-Benzyloxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester

5   (8)

Commercially available DL-o-tyrosine **1** (Fluka) is treated with L-aminoacid oxidase and

oxygen according to the procedure of Sun et al. (J. Med. Chem. 1998, 41, 1034-1041) to

afford the D-o-tyrosine **2**. Reaction with di-t-butyl-dicarbonate in the presence of base affords

10   the boc protected amino acid **3** (J. Med. Chem. 1998, 41, 1034-1041). The boc protected

acid **3** is then treated with benzyl bromide in the presence of potassium carbonate to afford the

benzyl ether **4** (J. Med. Chem. 1998, 41, 1034-1041). The four step sequence reported for

the preparation of the corresponding epoxide of phenylalanine (see J. Med. Chem. 1994, 37,

1758-1768) is used to prepare the desired epoxides. Thus, the acid **4** is treated with

15   isobutylchloroformate in the presence of N-methylmorpholine to afford the mixed anhydride

which is then treated with diazomethane to afford the α-diazoketone **5** (see scheme 1). The

ketone **5** is treated with HCl to form the α-chloroketone **6** which is then reduced with sodium

borohydride to form the chloro alcohol **7**. The 2S, 3R diastereoisomer is separated by

chromatography and treated with base (e.g. potassium hydroxide) to afford the epoxide **8**.

20

Commercially available DL-m-tyrosine **9** (Aldrich) is resolved by treatment with α-

chymotrypsin to afford D-m-tyrosine **10** (Recl.: J. R. Neth. Chem. Soc. 1984, 103, 4, p110-

111.) (Scheme 2). The tyrosine **10** is then treated in the same manner as the D-o-tyrosine

(Scheme 1) to form the m-benzyloxy epoxide **11**.

25

The Boc-D-Tyr(Bzl)-OH acid is commerically available (Bachem) and is treated according to

the four step procedure in Scheme 1 to generate the p-benzyloxy epoxide **13** shown in Scheme

3.

30   Example 2

Scheme 3 : Example, {4-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-

[1,2,4]triazepan-5-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester

The boc protected benzylhydrazine 12 is prepared by condensation of boc-carbazate with

benzaldehyde followed by catalytic hydrogenolysis (J. Chem. Soc. Perkin Trans. I 1975, 1712-

1720). Treatment of the epoxide 13 with the boc protected benzylhydrazine 12 affords the

5   alcohol 14 (J. Med. Chem. 1996, 39, 392-397). Benzylation of the secondary alcohol with

benzylchloride in the presence of base (Green) affords the benzylether 15. Deprotection of the

BOC groups with trifluoroacetic acid yields the diamine 16 (Green). CDI mediated cyclization

affords the cyclic triazacycloheptanone 17 (J. Med. Chem. 1996, 39, 392-397). Alkyation of

the nitrogens with [2-(4-chloromethyl-2-methoxy-phenoxymethoxy)-ethyl]-trimethyl-silane

10   (prepared according to the reference J. Med. Chem. 1996, 39, 392-397) affords the bis-

substituted triazacycloheptanone 18 (J. Med. Chem. 1996, 39, 392-397). Catalytic

hydrogenolysis affords the unprotected phenol 19 (Green) which upon alkylation with

trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base

(e.g. cesium carbonate) yields the dibenzyl phosphonate 20. Removal of the silyl protecting

15   groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl

phosphonate ester product 21 (J. Med. Chem. 1996, 39, 392-397).

The meta substituted analog {3-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-

3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester or the

ortho analog, {2-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-

20   [1,2,4]triazepan-5-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester, are prepared

using the same methods except replacing the p-benzyloxyepoxide 13 with the meta- and ortho-

substituted benzyloxy epoxides, 11 and 8, respectively.

Example 3

25   Scheme 4 : Example, {4-[5-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-

[1,2,4]triazepan-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (30)

p-Benzyloxybenzaldehyde 22 is treated with boc-carbazate and then reduced by catalytic

hydrogenolysis to afford the hydrazine 23 (J. Chem. Soc. Perkin Trans. I 1975, 1712-1720).

30   The Boc epoxide 25 is prepared from the corresponding CBZ epoxide 24 by catalytic

hydrogenolysis followed by treatment with BOC anhydride (Green). The CBZ- epoxide 24 is

prepared according to the procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397).

Treatment of the epoxide 25 with the hydrazine 23 affords the alcohol 26. The alcohol 26 is treated with benzyl bromide in the presence of base (e.g. cesium carbonate) to afford the dibenzyl compound 27 (Green). The Boc groups are then removed using trifluoroacetic acid to yield diamine 28 (Green). Subjecting the diamine 28 to the same procedures shown in

5   Scheme 1 then affords the dibenzyl phosphonate ester 29. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 30 (*J. Med. Chem.* 1996, 39, 392-397).

The corresponding meta- and ortho- analogs are prepared using the same procedures as in Scheme 4 except substituting p-benzyloxybenzaldehyde with m- or o-

10   benzyloxybenzaldehyde respectively.

Example 4

Scheme 5: {3-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilanyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester

15   (36)

The SEM protected triazacycloheptanone 31 is prepared according to the reported procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397). Regioselective alkylation by treatment of the triazacycloheptanone with m-benzyloxybenzylchloride and sodium hydride in DMF affords 32 which is then alkylated a second time under similar conditions to afford the

20   bis-substituted compound 33 (J. Med. Chem. 1996, 39, 392-397). Catalytic hydrogenolysis affords the phenol 34 (Green). Alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester using the standard conditions affords the dibenzyl ester 35. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 36 (J. Med. Chem. 1996, 39, 392-397).

25   Ortho analog {2-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilanyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog {4-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilanyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using the same procedures except substituting o-

30   benzyloxybenzylchloride and p-benzyloxybenzylchloride respectively, for the m-benzyloxybenzylchloride. O-benzyloxybenzylchloride is prepared from o-

benzyloxybenzaldehyde by reduction with sodium borohydride and then treatment with
methanesulfonylchloride (J. Med. Chem. 1996, 39, 392-397).

Example 5

5   Scheme 6: {3-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-
     [1,2,4]triazepan-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (41)

         The SEM protected triazacycloheptanone 31 is prepared according to the reported
     procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397). Regioselective alkylation by
     treatment of the triazacycloheptanone with SEM protected benzylchloride and sodium hydride

10   in DMF affords 37 which is then alkylated with m-benzyloxybenzylchloride under similar
     conditions to afford the bis-substituted compound 38 (J. Med. Chem. 1996, 39, 392-397).
     Catalytic hydrogenolysis affords the phenol 39 (Green). Alkylation with trifluoro-
     methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester using the standard conditions
     affords the dibenzyl ester 40. Removal of the silyl protecting groups using trimethylsilyl

15   chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 41 (J.
     Med. Chem. 1996, 39, 392-397).

     Ortho analog, {2-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-
     [1,2,4]triazepan-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog,

20   {4-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-
     ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using the same
     procedures except substituting o-benzyloxybenzylchloride and p-benzyloxybenzylchloride
     respectively, for the m-benzyloxybenzylchloride.

<u>Scheme General Section</u>

General aspects of these exemplary methods are described below and in the Example. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

5   The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting

10   compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M),

15   temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the

20   conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter

25   "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step

30   or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or

35   low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.
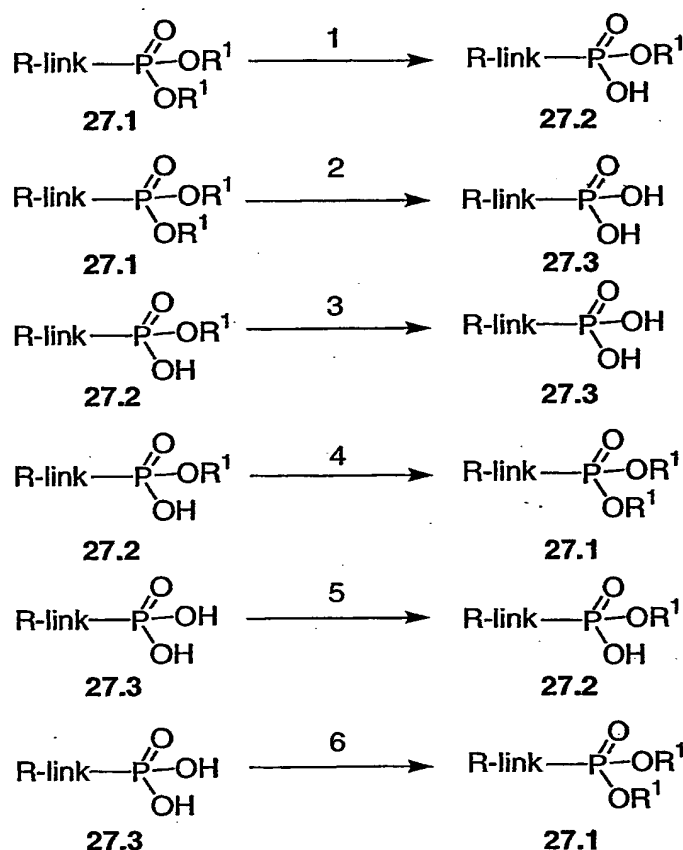
Another class of separation methods involves treatment of a mixture with a reagent

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selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic

5   material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in

10   acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described

15   in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Scheme 1001

R-link—P(=O)(OR^1)—OR^1 with OR^1 **27.1** →(1)→ R-link—P(=O)(OR^1)—OR^1 with OH **27.2**

R-link—P(=O)(OR^1)—OR^1 with OR^1 **27.1** →(2)→ R-link—P(=O)—OH with OH **27.3**

R-link—P(=O)(OR^1)—OR^1 with OH **27.2** →(3)→ R-link—P(=O)—OH with OH **27.3**

R-link—P(=O)(OR^1)—OR^1 with OH **27.2** →(4)→ R-link—P(=O)(OR^1)—OR^1 with OR^1 **27.1**

R-link—P(=O)—OH with OH **27.3** →(5)→ R-link—P(=O)(OR^1)—OR^1 with OH **27.2**

R-link—P(=O)—OH with OH **27.3** →(6)→ R-link—P(=O)(OR^1)—OR^1 with OR^1 **27.1**

Scheme 1001 shows the interconversions of certain phosphonate compounds: acids -

5    $P(O)(OH)_2$; mono-esters -$P(O)(OR_1)(OH)$; and diesters -$P(O)(OR_1)_2$ in which the R^1 groups

are independently selected, and defined herein before, and the phosphorus is attached through

a carbon moiety (link, i.e. linker), which is attached to the rest of the molecule, e.g. drug or

drug intermediate (R). The R^1 groups attached to the phosphonate esters in Scheme 1001

may be changed using established chemical transformations. The interconversions may be

10   carried out in the precursor compounds or the final products using the methods described

below. The methods employed for a given phosphonate transformation depend on the nature

of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in

Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate

15   monoester **27.2** (Scheme 1001, Reaction 1) can be accomplished by a number of methods.

For example, the ester **27.1** in which R^1 is an arylalkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about

5   110°C. The conversion of the diester **27.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **27.2** in which one of the groups R^1 is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in

10   which R^1 is alkyl, by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure

15   described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme 1001, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for

20   example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which R^1 is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **27.2** in which R^1 is alkenyl

25   such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of

30   phosphonate esters **27.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme 1001, Reaction 4) in which the newly introduced R^1 group is alkyl, arylalkyl, or

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haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate 27.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is

5   preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl

10   phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 27.1 to the diester 27.1 can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 27.2 can be transformed into the phosphonate diester 27.1, in which

15   the introduced R¹ group is alkenyl or arylalkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or arylalkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester

20   27.2 is transformed into the chloro analog -P(O)(OR¹)Cl by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product -P(O)(OR¹)Cl is then reacted with the hydroxy compound R¹OH, in the presence of a base such as triethylamine, to afford the phosphonate diester 27.1.

25   A phosphonic acid -P(O)(OH)₂ can be transformed into a phosphonate monoester -P(O)(OR¹)(OH) (Scheme 1001, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester -P(O)(OR¹)₂ 27.1, except that only one molar proportion of the component R¹OH or R¹Br is employed.

           A phosphonic acid -P(O)(OH)₂ 27.3 can be transformed into a phosphonate diester

30   -P(O)(OR¹)₂ 27.1 (Scheme 1, Reaction 6) by a coupling reaction with the hydroxy compound R¹OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which

R^1 is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar

5   organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester 27.1.

Amino alkyl phosphonate compounds 809:

10
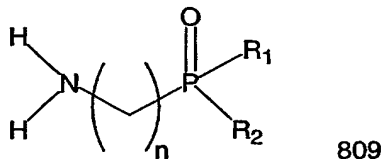
are a generic representative of compounds 811, 813, 814, 816 and 818. Some methods to prepare embodiments of 809 are shown in Scheme 1002. Commercial amino phosphonic acid 810 was protected as carbamate 811. The phosphonic acid 811 was converted to phosphonate 812 upon treatment with ROH in the presence of DCC or other conventional

15   coupling reagents. Coupling of phosphonic acid 811 with esters of amino acid 820 provided bisamidate 817. Conversion of acid 811 to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid 814 (Cbz = $C_6H_5CH_2C(O)-$), which was then transformed to mono-phosphonic amidate 815. Carbamates 813, 816 and 818 were converted to their corresponding amines upon hydrogenation. Compounds 811, 813, 814, 816 and 818 are

20   useful intermediates to form the phosphonate compounds of the invention.

Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters.

25   A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in J. Gen. Chem. USSR, 1983, 53, 480, Zh. Obschei Khim., 1958, 28, 1063, or J. Org. Chem., 1994, 59, 6144, or by reaction with oxalyl chloride, as described in J. Am. Chem. Soc., 1994, 116, 3251, or J. Org. Chem., 1994, 59,

5   6144, or by reaction with phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or in J. Med. Chem., 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

10   Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in J. Chem. Soc., Chem. Comm., 1991, 312, or Nucleosides Nucleotides 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in J. Med. Chem. 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in

15   Tet. Lett., 1996, 7857, or Bioorg. Med. Chem. Lett., 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters. Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for

20   example, in J. Chem. Soc., Chem. Comm., 1991, 312, or J. Med. Chem., 1980, 23, 1299 or Coll. Czech. Chem. Comm., 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in Tet. Lett., 2001, 42, 8841, or Nucleosides Nucleotides, 2000, 19, 1885.

25   A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in J. Org. Chem., 1995, 60, 5214, and J. Med. Chem., 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in J. Med. Chem., 1996, 39, 4958, diphenylphosphoryl azide, as described in J. Org. Chem., 1984, 49, 1158, 1-(2,4,6-

30   triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in Bioorg. Med. Chem. Lett., 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in Tet. Lett., 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-

dioxaphosphinane, as described in Nucleosides Nucleotides 1995, 14, 871, and diphenyl chlorophosphate, as described in J. Med. Chem., 1988, 31, 1305.

5 Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in Org. Lett., 2001, 3, 643, or J. Med. Chem., 1997, 40, 3842.

10 Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in Anal. Chem., 1987, 59, 1056, or J. Chem. Soc. Perkin Trans., I, 1993, 19, 2303, or J. Med. Chem., 1995, 38, 1372, or Tet. Lett., 2002, 43, 1161.

15 Schemes 1 - 4 illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme 1), phosphoroamidates (Scheme 2), phosphonate monoesters (Scheme 3) and phosphonate diesters, (Scheme 4).

Scheme 1 illustrates various methods for the conversion of phosphonate diesters **1.1** into phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed,
20 either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these transformations are described above. The monoester **1.2** is converted into the monoamidate **1.3** by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an alkylene moiety such as, for example, $CHCH_3$, $CHPr^J$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the like, or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The
25 reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in J. Am. Chem. Soc., 1957, 79, 3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **1.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in J. Org. Chem., 1995, 60, 5214, Aldrithiol,
30 PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **1.2** and **1.9** are transformed into the monoamidate **1.3** by means of a Mitsonobu reaction. The preparation of amidates by means of the Mitsonobu reaction is described in J. Med. Chem., 1995, 38, 2742. Equimolar amounts of the reactants are

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combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **1.3** is then transformed. into amidate phosphonic acid **1.4**. The conditions used for the hydrolysis reaction depend on the nature of the R¹ group, as described previously. The phosphonic acid amidate **1.4** is then

5   reacted with an aminoester **1.9**, as described above, to yield the bisamidate product **1.5**, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme 1, Example 1. In this procedure, a dibenzyl phosphonate **1.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux,

10   as described in J. Org. Chem., 1995, 60, 2946, to afford the monobenzyl phosphonate **1.15**. The product is then reacted with equimolar amounts of ethyl alaninate **1.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product **1.17**. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **1.18**. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate

15   **1.19**, triphenyl phosphine and diethylazodicarboxylate, as described in J. Med. Chem., 1995, 38, 2742, to produce the bisamidate product **1.20**.

Using the above procedures, but employing, in place of ethyl leucinate **1.19** or ethyl alaninate **1.16**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

20

Alternatively, the phosphonic acid **1.6** is converted into the bisamidate **1.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **1.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

25   An example of the method is shown in Scheme 1, Example 2. In this procedure, a phosphonic acid **1.6** is reacted in pyridine solution with excess ethyl phenylalaninate **1.21** and dicyclohexylcarbodiimide, for example as described in J. Chem. Soc., Chem. Comm., 1991, 1063, to give the bisamidate product **1.22**.

30 .   Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as

5   described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in J. Med. Chem., 2002, 45, 1284 and in J. Chem. Soc. Chem. Comm., 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in Nucleosides and Nucleotides, 2000, 10, 1885. The activated product

10   is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

15   Examples of these methods are shown in Scheme 1, Examples 3 and 5. In the procedure illustrated in Scheme 1, Example 3, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in Zh. Obschei Khim., 1958, 28, 1063, to give the dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with

20   butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

25   In the procedure illustrated in Scheme 1, Example 5, the phosphonic acid **1.6** is reacted, as described in J. Chem. Soc. Chem. Comm., 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated

30   intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate 1.33 or ethyl N-methylalaninate 1.33a, different aminoesters 1.9, the corresponding products 1.5 are obtained.

5   The intermediate monoamidate 1.3 is also prepared from the monoester 1.2 by first converting the monoester into the activated derivative 1.8 in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product 1.8 is then reacted with an aminoester 1.9 in the presence of a base such as pyridine, to give an intermediate monoamidate product 1.3. The latter compound is then converted, by removal

10   of the R^1 group and coupling of the product with the aminoester 1.9, as described above, into the bisamidate 1.5.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative 1.26, is shown in Scheme 1, Example 4. In this procedure, the phosphonic

15   monobenzyl ester 1.15 is reacted, in dichloromethane, with thionyl chloride, as described in Tet. Let., 1994, 35, 4097, to afford the phosphoryl chloride 1.26. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate 1.27 to yield the monoamidate product 1.28. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the

20   monoacid product 1.29. The product is subjected to a Mitsonobu coupling procedure, with equimolar amounts of butyl alaninate 1.30, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product 1.31.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate

25   1.27 or butyl alaninate 1.30, different aminoesters 1.9, the corresponding products 1.5 are obtained.

The activated phosphonic acid derivative 1.7 is also converted into the bisamidate 1.5 via the diamino compound 1.10. The conversion of activated phosphonic acid derivatives such as

30   phosphoryl chlorides into the corresponding amino analogs 1.10, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound 1.10 is then reacted at elevated temperature with a haloester

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1.12, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate 1.5.

An example of this procedure is shown in Scheme 1, Example 6. In this method, a dichlorophosphonate 1.23 is reacted with ammonia to afford the diamide 1.37. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate 1.38, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product 1.39.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate 1.38, different haloesters 1.12 the corresponding products 1.5 are obtained.

The procedures shown in Scheme 1 are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme 1, Example 7 illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide 1.32 is reacted with propyl tyrosinate 1.40, as described in Example 5, to yield the monoamidate 1.41. The product is reacted with carbonyl diimidazole to give the imidazolide 1.42, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product 1.43.

Using the above procedures, but employing, in place of propyl tyrosinate 1.40, different aminoesters 1.9, the corresponding products 1.5 are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

Scheme 2 illustrates methods for the preparation of phosphonate monoamidates.

In one procedure, a phosphonate monoester 1.1 is converted, as described in Scheme 1, into the activated derivative 1.8. This compound is then reacted, as described above, with an aminoester 1.9, in the presence of a base, to afford the monoamidate product 2.1.

The procedure is illustrated in Scheme 2, Example 1. In this method, a monophenyl phosphonate 2.7 is reacted with, for example, thionyl chloride, as described in J. Gen. Chem.

USSR., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as described in Scheme **1**, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme **1**, with an aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described in Scheme **1** for the coupling of amines and phosphonic acids.

Scheme 1
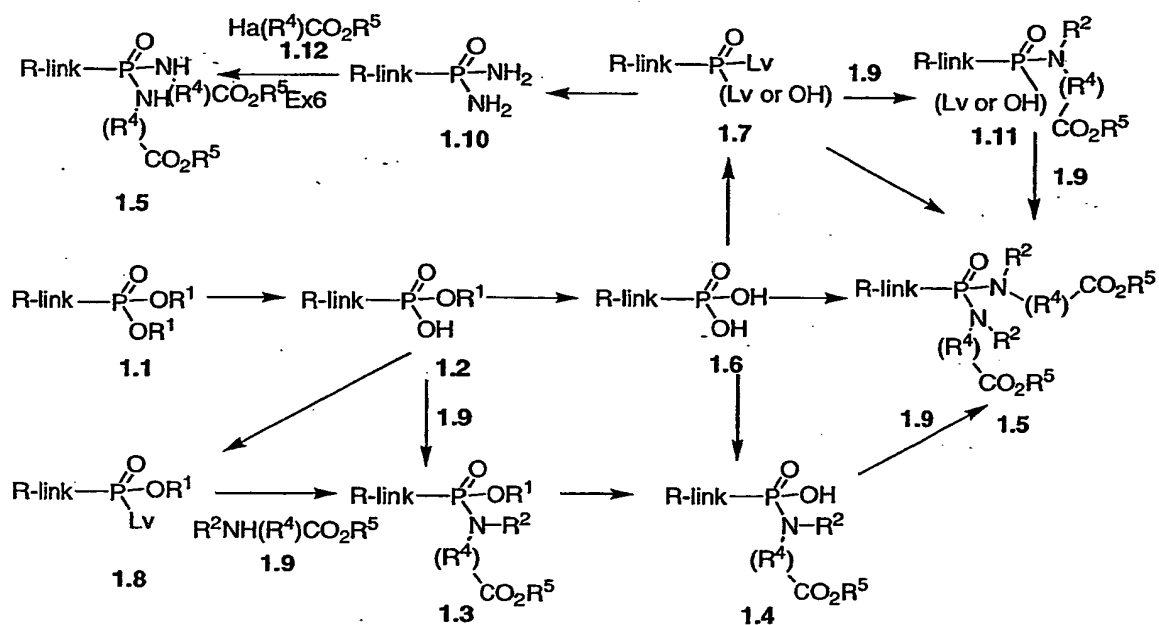
Scheme 1 Example 1
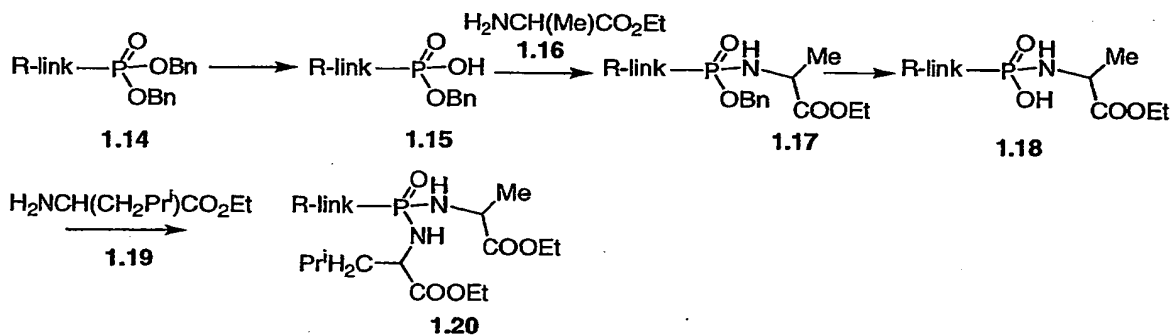
Scheme 1 Example 2

Scheme 1 Example 3

R-link—P(=O)(OH)OH → R-link—P(=O)(Cl)Cl

1.6   **1.23**

$H_2NCH(CH_2OH)CO_2Bu$
1.24

→ R-link—P(=O)(NH—CH(CH_2OH)CO_2Bu)(NH—CH(CH_2OH)CO_2Bu)

1.25

Scheme 1 Example 4

R-link—P(=O)(OBn)OH → R-link—P(=O)(OBn)Cl

1.15   **1.26**

$H_2NCH_2CH(Me)CO_2Et$
1.27

→ R-link—P(=O)(OBn)NH—CH_2CH(Me)CO_2Et

1.28

→ R-link—P(=O)(OH)NH—CH_2CH(Me)CO_2Et

1.29

$H_2NCH(Me)CO_2Bu$
1.30

→ R-link—P(=O)(NH—CH(Me)CO_2Bu)(NH—CH_2CH(Me)CO_2Et)

1.31

Scheme 1 Example 5

R-link—P(=O)(OH)OH → R-link—P(=O)(OH)Im

1.6   **1.32**

$H_2NCH(Me)CO_2Et$
1.33

→ R-link—P(=O)(OH)NH—CH(Me)CO_2Et →

1.34

R-link—P(=O)(Im)NH—CH(Me)CO_2Et

1.35

$MeNHCH(Me)CO_2Et$
1.33a

→ R-link—P(=O)(N(Me)—CH(Me)CO_2Et)(NH—CH(Me)CO_2Et)

1.36

Scheme 1 Example 6

R-link—P(=O)(Cl)Cl → R-link—P(=O)(NH_2)NH_2

1.23   **1.37**

$BrCH(Pr^i)CO_2Et$
1.38

→ R-link—P(=O)(NH—CH(Pr^i)CO_2Et)(NH—CH(Pr^i)CO_2Et)

1.39

Scheme 1 Example 7

Examples of this method are shown in Scheme 2, Examples and 2 and 3. In the sequence shown in Example 2, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as described in Tet. Lett., 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme 2, Example 3, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme 1, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme 2, Example 4. In this sequence, the monophenyl phosphoryl

chloride **2.18** is reacted, as described in Scheme 1, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**. Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**,

5   different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-

10   displacement product **1.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

The method is illustrated in Scheme 2, Example 5. In this method, the phosphoryl dichloride

15   **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

20   Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

Scheme 2
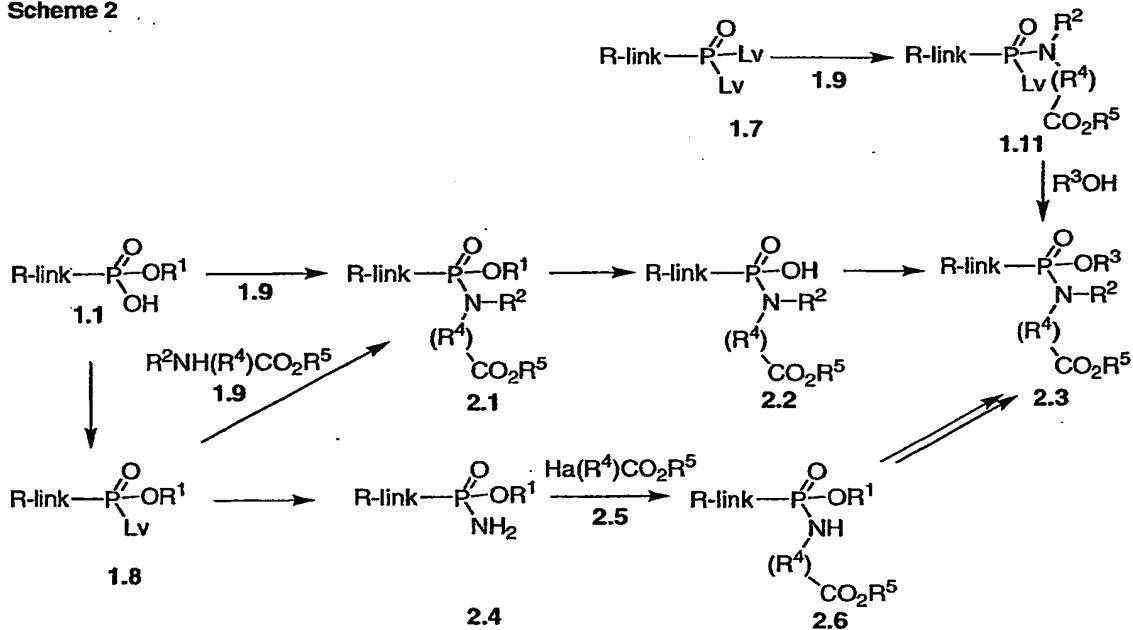
Scheme 2 Example 1
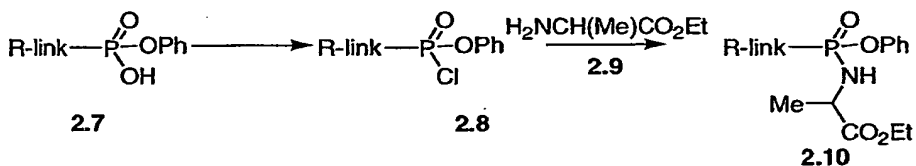
Scheme 2 Example 2
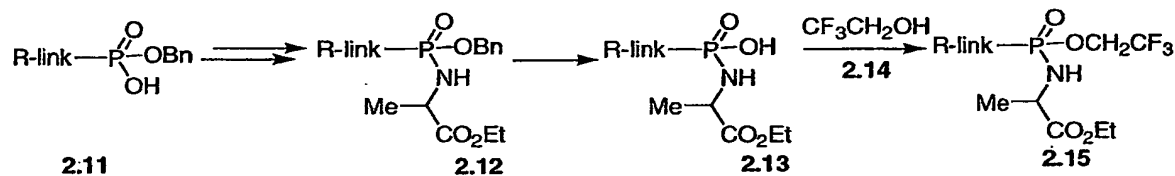
Scheme 2 Example 3
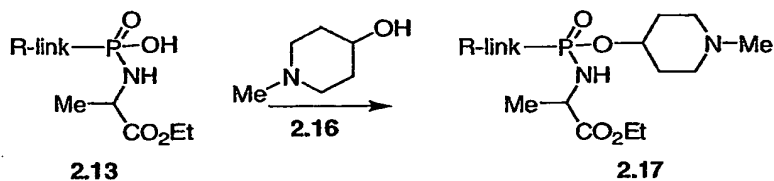
Scheme 2 Example 4
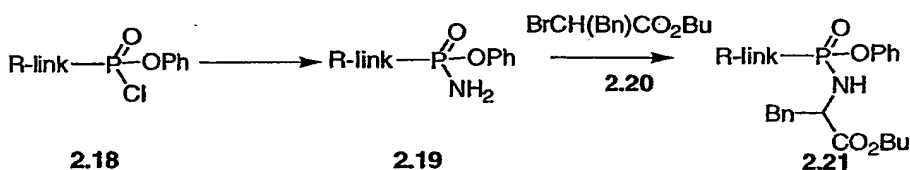
Scheme 2 Example 5
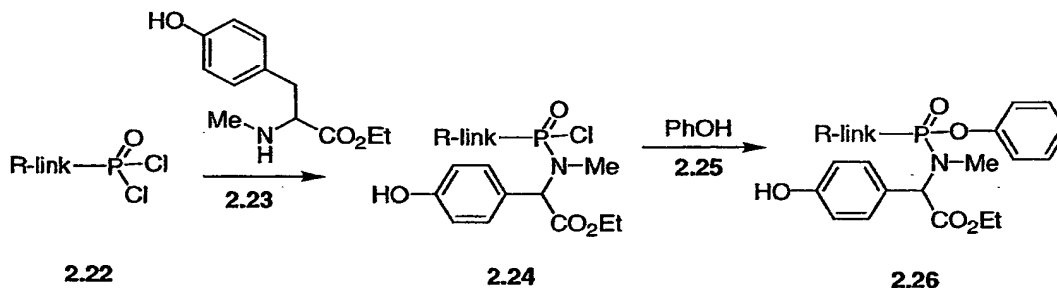
Scheme 3 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

5   In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme 1. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described

10   in Tet., 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme 3, Example 1. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl

15   carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

20

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as described in Org. Lett., 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate,

5   to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **3.4**.

10   The procedure is illustrated in Scheme 3, Example 2. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and

15   produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-

20   hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^3OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated

25   compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in Nucleosides and Nucleotides, 2000, 19, 1885, or with carbonyl diimidazole, as described in J. Med. Chem., 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**,

30   as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme 3, Example 3. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl

chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

5 Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already

10 incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

15 The method is illustrated in Scheme 3, Example 4. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in J. Med. Chem., 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the

20 mixed diester product **3.25**.

Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

25 The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in Anal. Chem., 1987, 59, 1056, or triethylamine, as described in J. Med. Chem., 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as

30 described in Syn. Comm., 1995, 25, 3565.

The method is illustrated in Scheme **3**, Example **5**. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

5   Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

Scheme 3
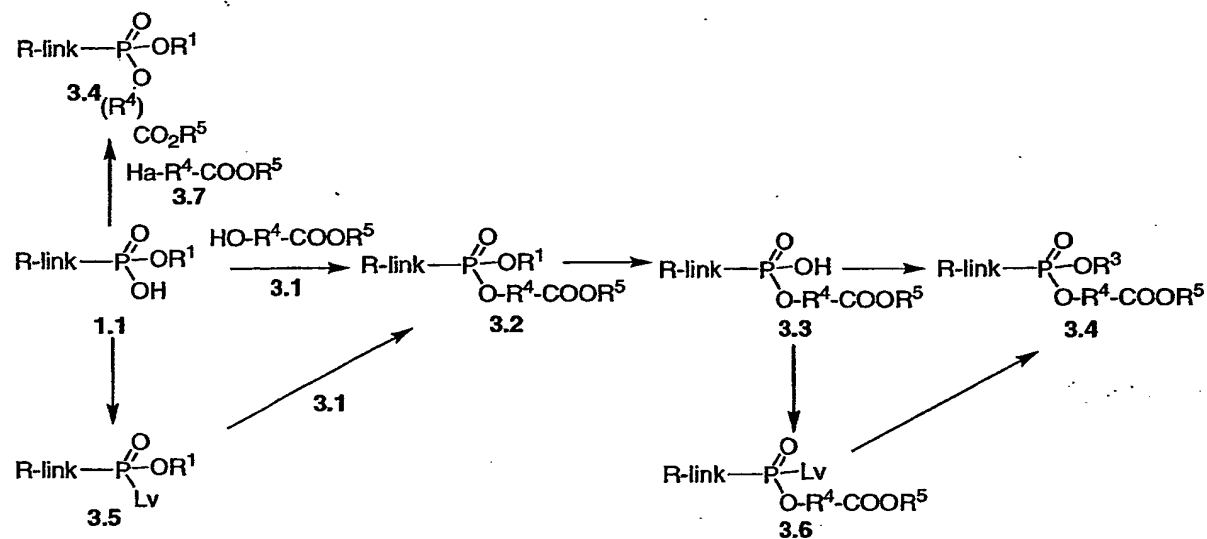
Scheme 3 Example 1
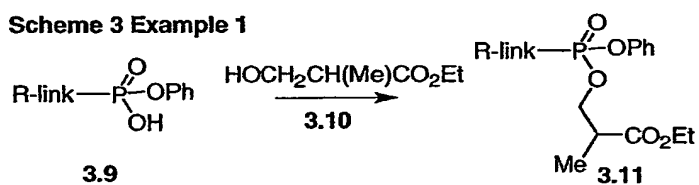
Scheme 3 Example 2
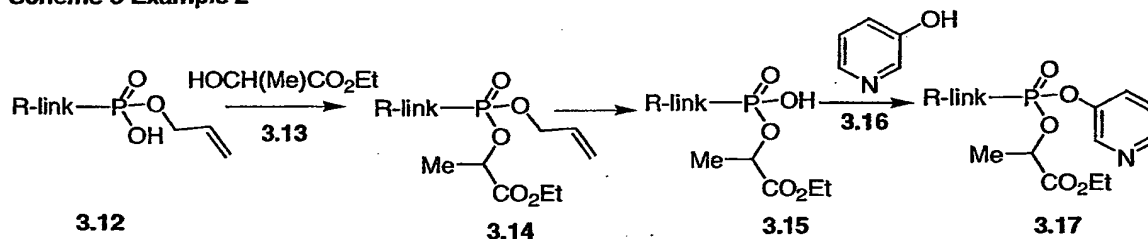
Scheme 3 Example 3

Scheme 3 Example 4

3.22   3.23   3.25

Scheme 3 Example 5

3.26   3.27   3.28
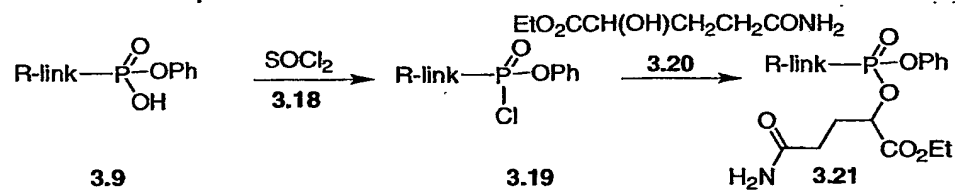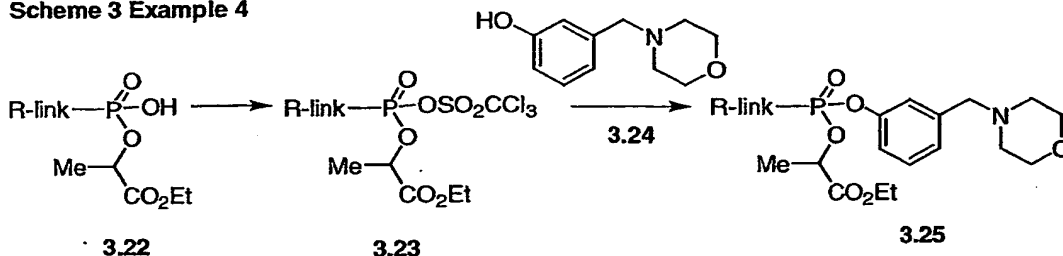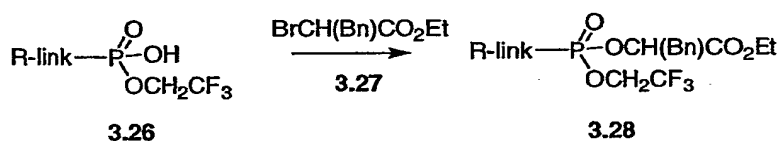
Scheme **4** illustrates methods for the preparation of phosphonate diesters in which both the
ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one
alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions
described previously in Schemes **1 - 3**, such as coupling reactions using dicyclohexyl
carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford
the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme **4**, Example **1**. In this procedure, the phosphonic acid
1.6 is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2
and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.
Using the above procedure, but employing, in place of butyl lactate **4.5**, different
hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a
haloester **4.1**. The alkylation reaction is performed as described in Scheme 3 for the
preparation of the esters **3.4**.

This method is illustrated in Scheme 4, Example 2. In this procedure, the phosphonic acid

1.6 is reacted with excess ethyl 3-bromo-2-methylpropionate 4.7 and diisopropylethylamine

in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce

5   the diester 4.8.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate

4.7, different haloesters 4.1, the corresponding products 4.3 are obtained.

The diesters 4.3 are also obtained by displacement reactions of activated derivatives 1.7 of

10   the phosphonic acid with the hydroxyesters 4.2. The displacement reaction is performed in a

polar solvent in the presence of a suitable base, as described in Scheme 3. The displacement

reaction is performed in the presence of an excess of the hydroxyester, to afford the diester

product 4.3 in which the ester substituents are identical, or sequentially with limited amounts

of different hydroxyesters, to prepare diesters 4.3 in which the ester substituents are different.

15   The methods are illustrated in Scheme 4, Examples 3 and 4. As shown in Example 3, the

phosphoryl dichloride 2.22 is reacted with three molar equivalents of ethyl 3-hydroxy-2-

(hydroxymethyl)propionate 4.9 in tetrahydrofuran containing potassium carbonate, to obtain

the diester product 4.10.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-

20   (hydroxymethyl)propionate 4.9, different hydroxyesters 4.2, the corresponding products 4.3

are obtained.

Scheme 4, Example 4 depicts the displacement reaction between equimolar amounts of the

phosphoryl dichloride 2.22 and ethyl 2-methyl-3-hydroxypropionate 4.11, to yield the

monoester product 4.12. The reaction is conducted in acetonitrile at 70°C in the presence of

25   diisopropylethylamine. The product 4.12 is then reacted, under the same conditions, with one

molar equivalent of ethyl lactate 4.13, to give the diester product 4.14.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate

4.11 and ethyl lactate 4.13, sequential reactions with different hydroxyesters 4.2, the

corresponding products 4.3 are obtained.
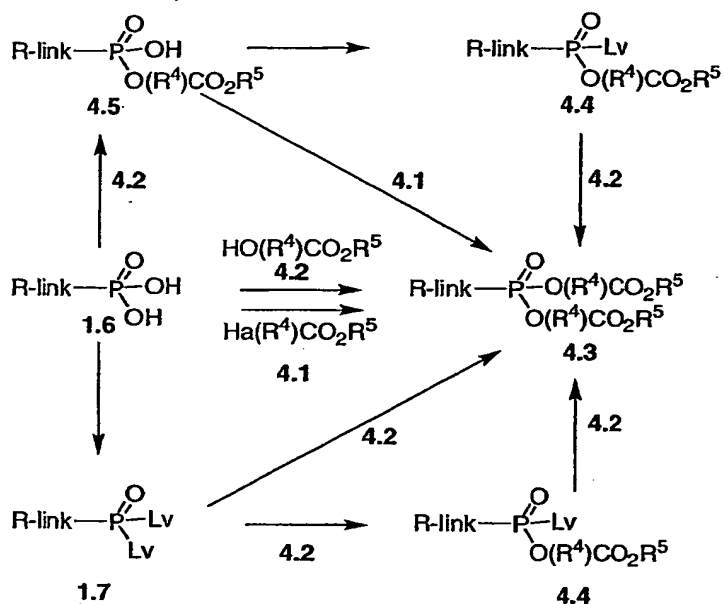
Scheme 4

Scheme 4 Example 1
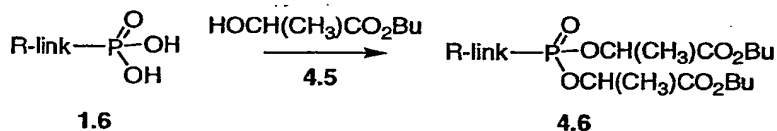
Scheme 4 Example 2
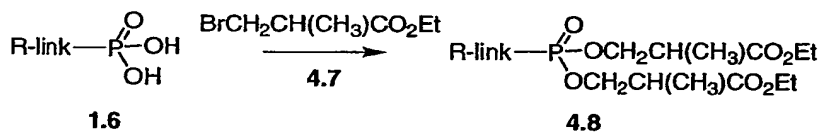
Scheme 4 Example 3
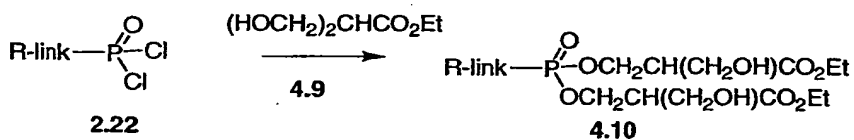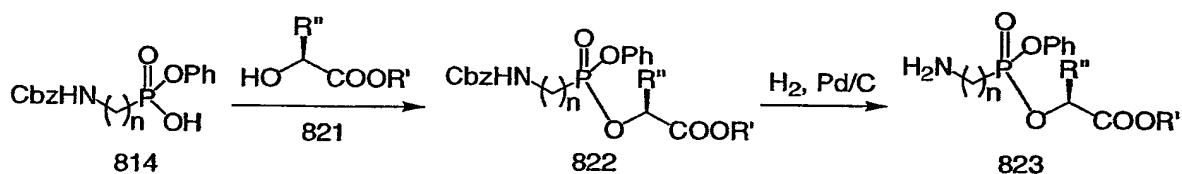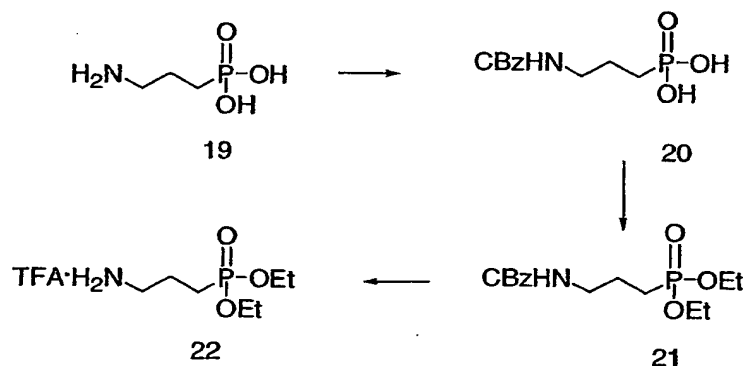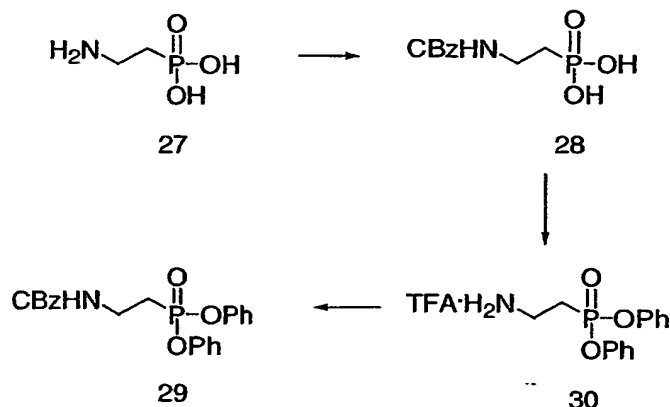

Scheme 4 Example 4

Scheme 1002

5
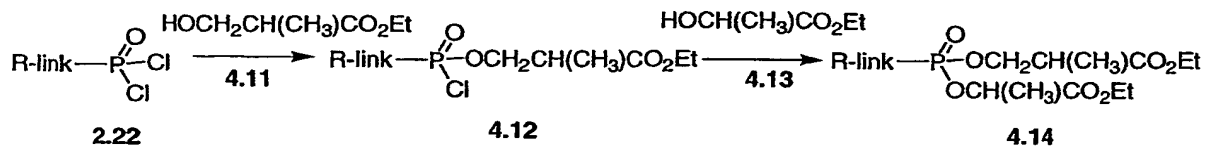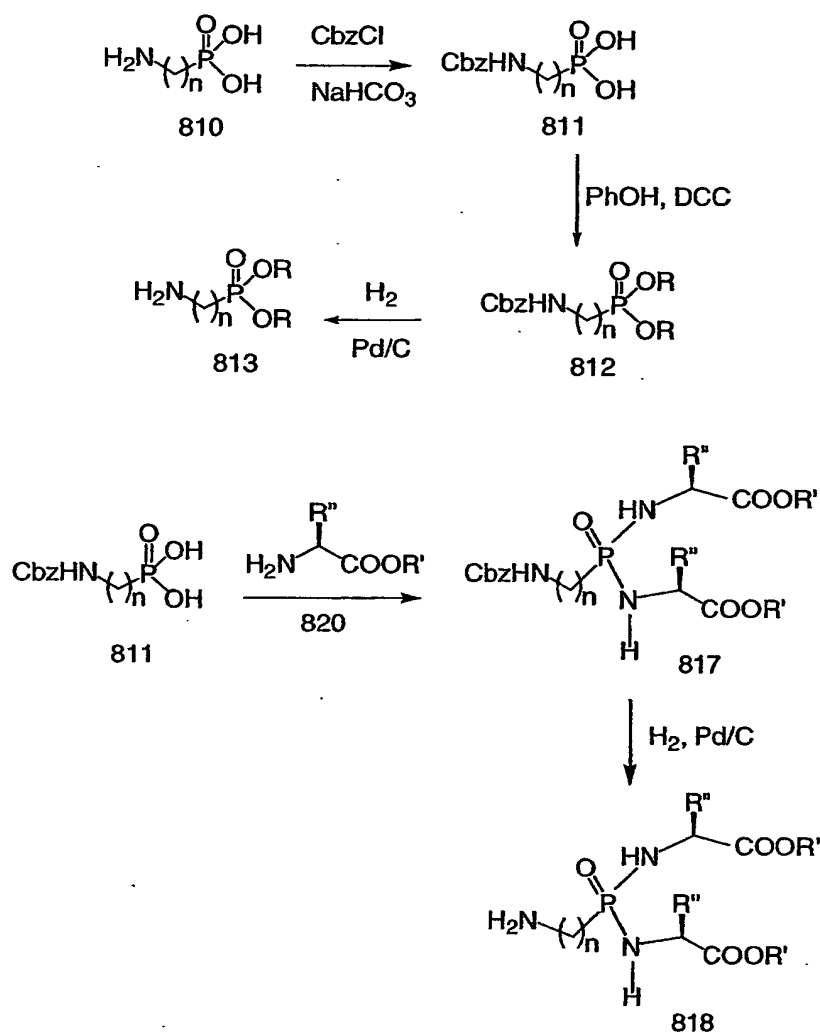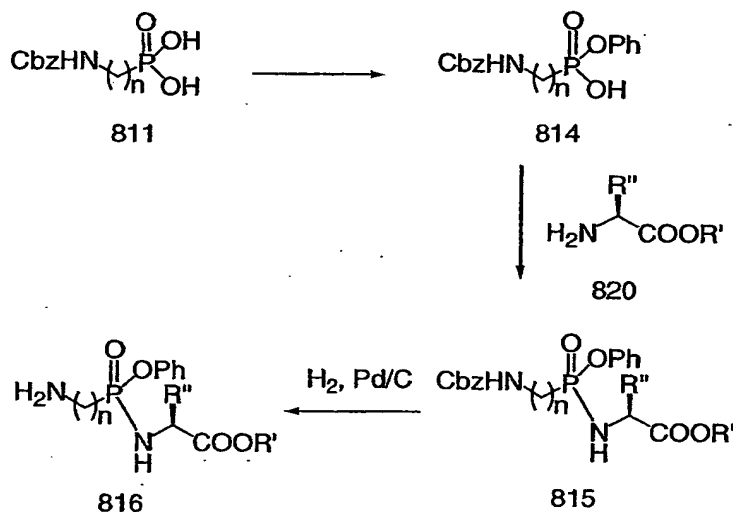
Following the similar procedures, replacement of amino acid esters 820 with lactates 821 (Scheme 1003) provides mono-phosphonic lactates 823. Lactates 823 are useful intermediates to form the phosphonate compounds of the invention.

5   Scheme 1003

10   Scheme 1004

Scheme 1005

27 → 28 → 30 → 29

Example 1

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1

5   mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction

mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O

and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting

colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g).

After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced

10   pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid (Scheme 1005).

To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added

phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the

reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with

CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with

15   EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried

over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was

chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29**

(2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in iPrOH (5 mL) was added

20   TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred

under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate

was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil

(Scheme 1005).

Scheme Section A

Exemplary methods of preparing the compounds of the invention are shown in Schemes 1-7 below. A detailed description of the methods is found in the Experimental section below.
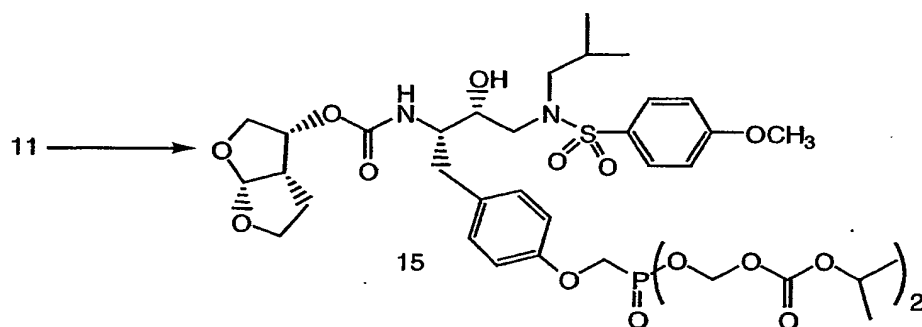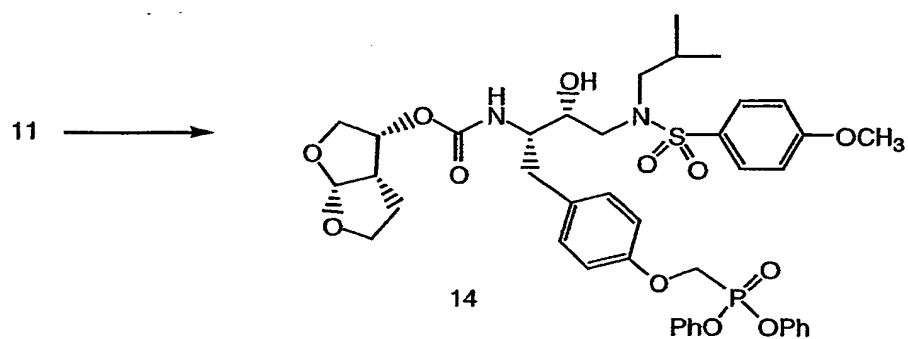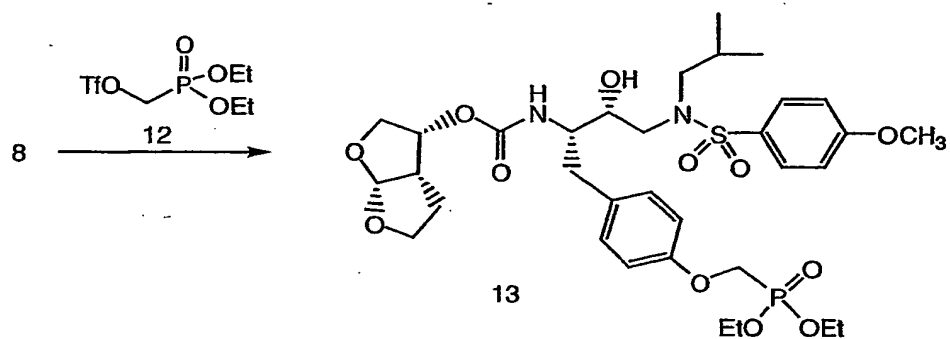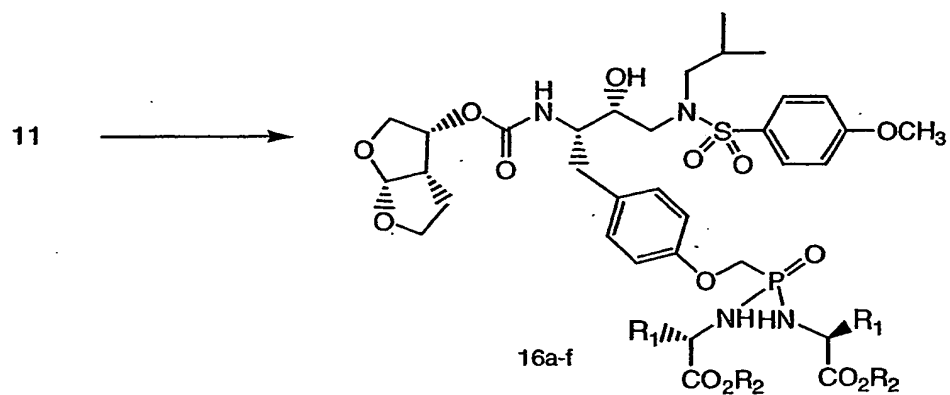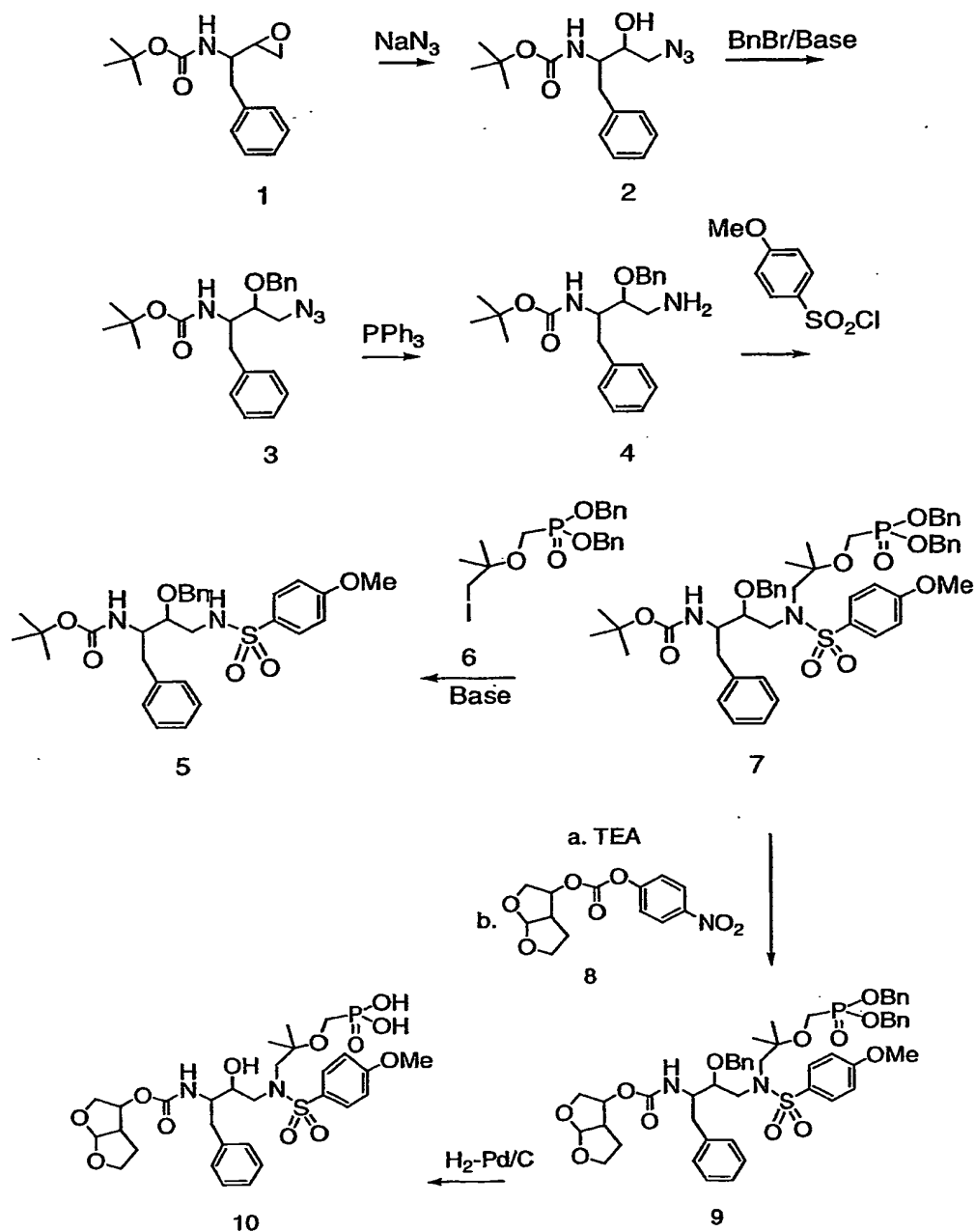
5

Scheme 1

Scheme 2

7

8   +   9

10

11

Scheme 3

13

14

15

Scheme 4

11 $\longrightarrow$

16a-f

Scheme 5

Scheme 6

P = *tert*-butyldimethylsilyl

Scheme 7

14   ⟶

29   ⟶

30
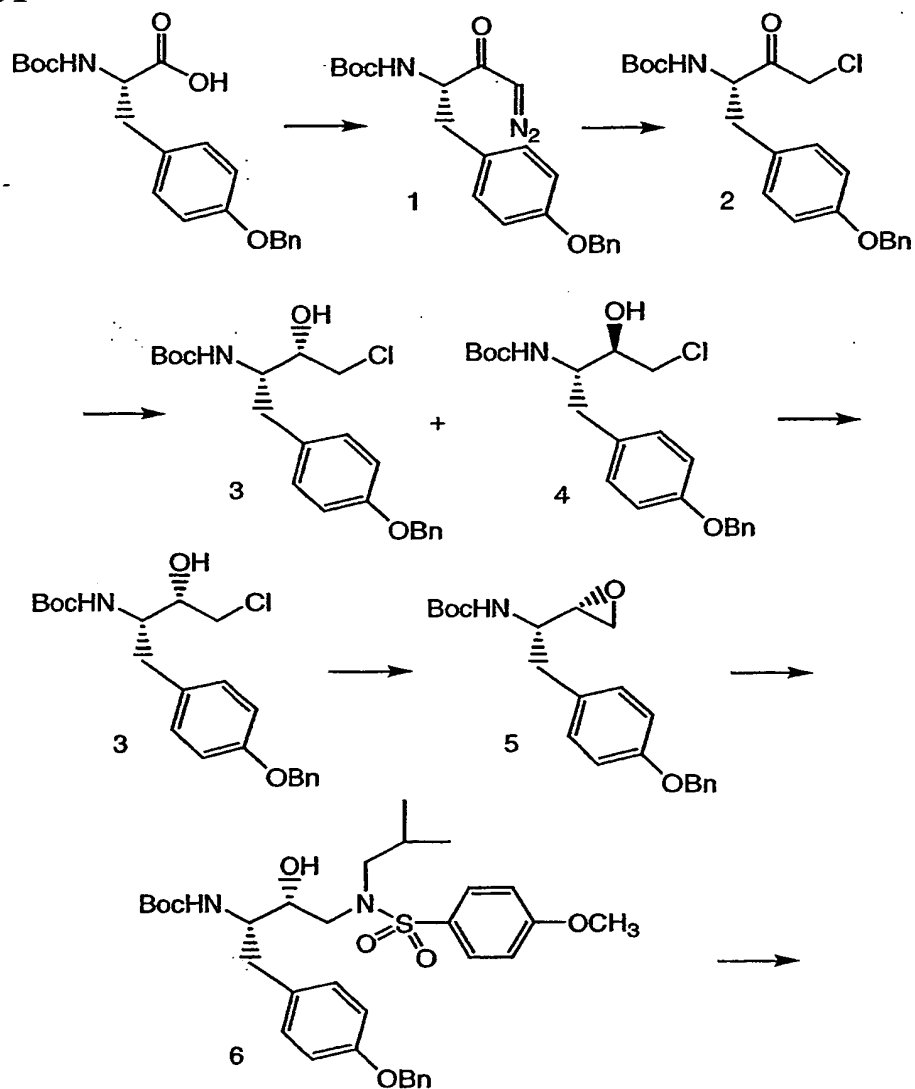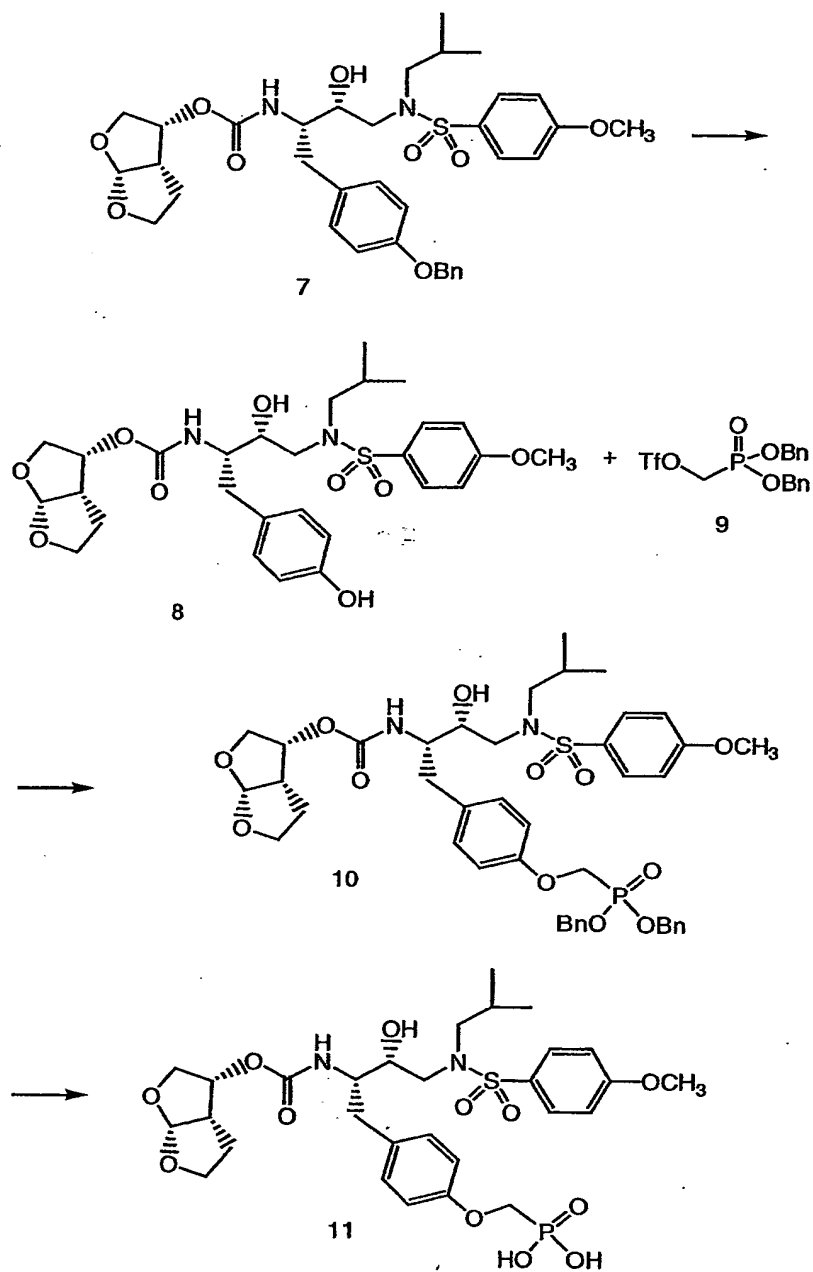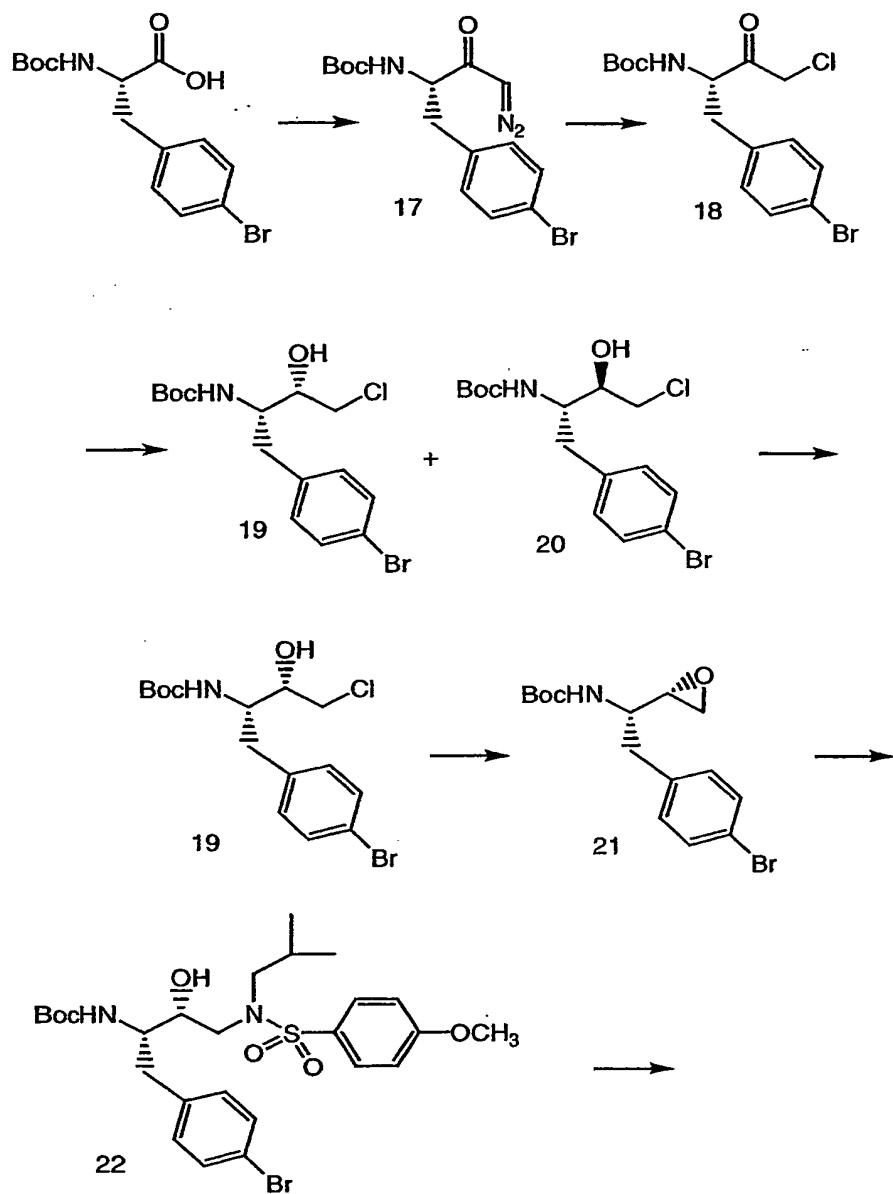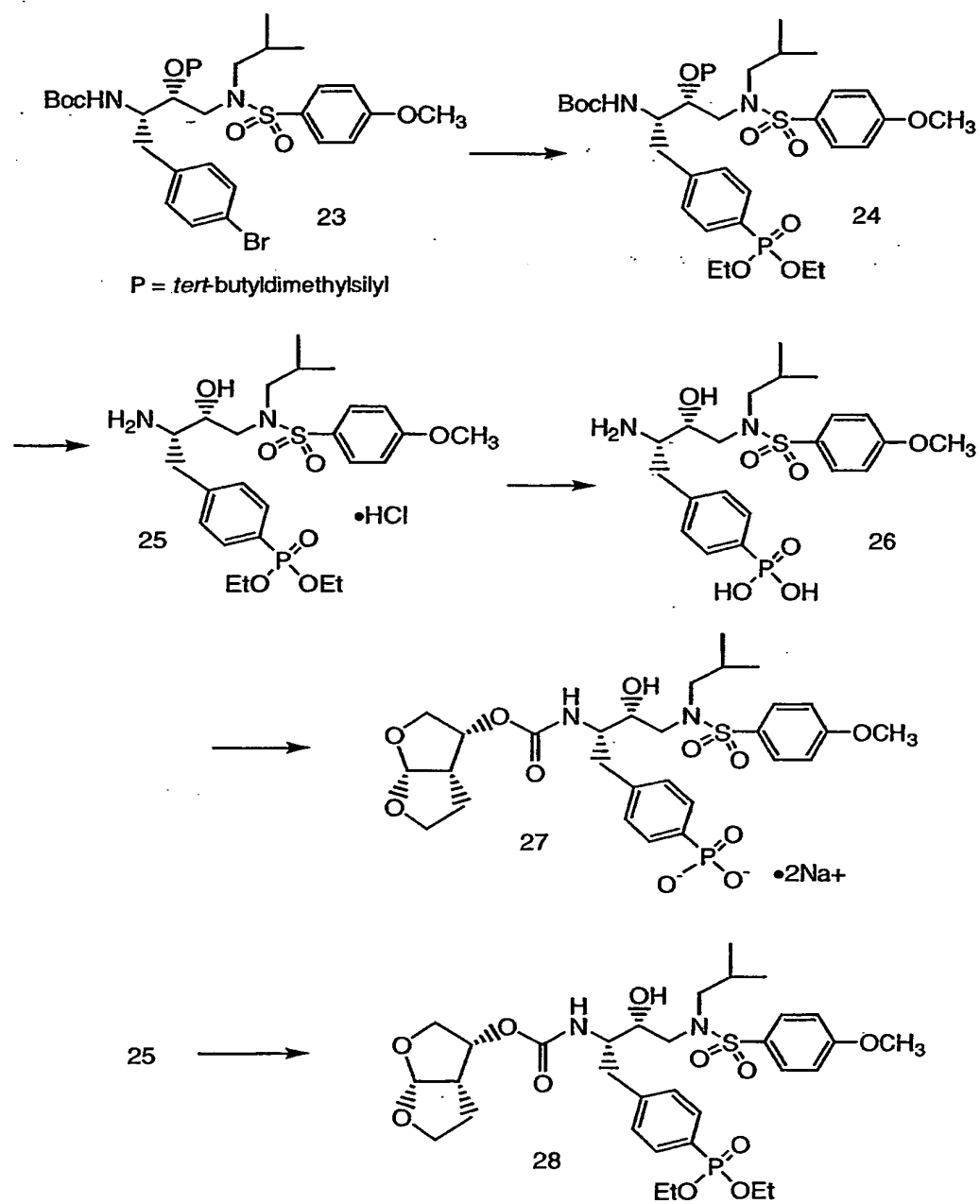
Scheme Section B

Alternative exemplary methods of preparing the compounds of the invention are shown in **Schemes 101-113** below.

5   **Scheme 101**

10

Treatment of commercially available epoxide 1 with sodium azide (Bioorg. & Med. Chem.

Lett., 5, 459, 1995) furnishes the azide intermediate 2. The free hydroxyl is converted to

benzyl ether 3 by treating it with benzyl bromide in the presence of base such as potassium

5   carbonate. Compound 4 is achieved by the reduction of the azide group with triphenyl

phosphine, as described in the publication Bioorg. & Med. Chem. Lett., 7, 1847, 1997.

Conversion of the amino group to its sulfonamide derivative 5 is achieved by treating the

amine with stoichiometric amounts of sulfonyl chloride. Regioselective alkylation is

performed (as shown in the article J. Med. Chem., 40, 2525, 1997) on the sulfonamide

10   nitrogen using the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the compound 7. Upon

TFA catalyzed deprotection of BOC group followed by the reaction with bisfuranyl carbonate

8 (for a similar coupling see, J. Med. Chem., 39, 3278, 1996) furnishes the compound 9.

Final deprotection of the protecting groups by catalytic hydrogenolysis result the compound

10.

Scheme 102

11   12   1

5

13
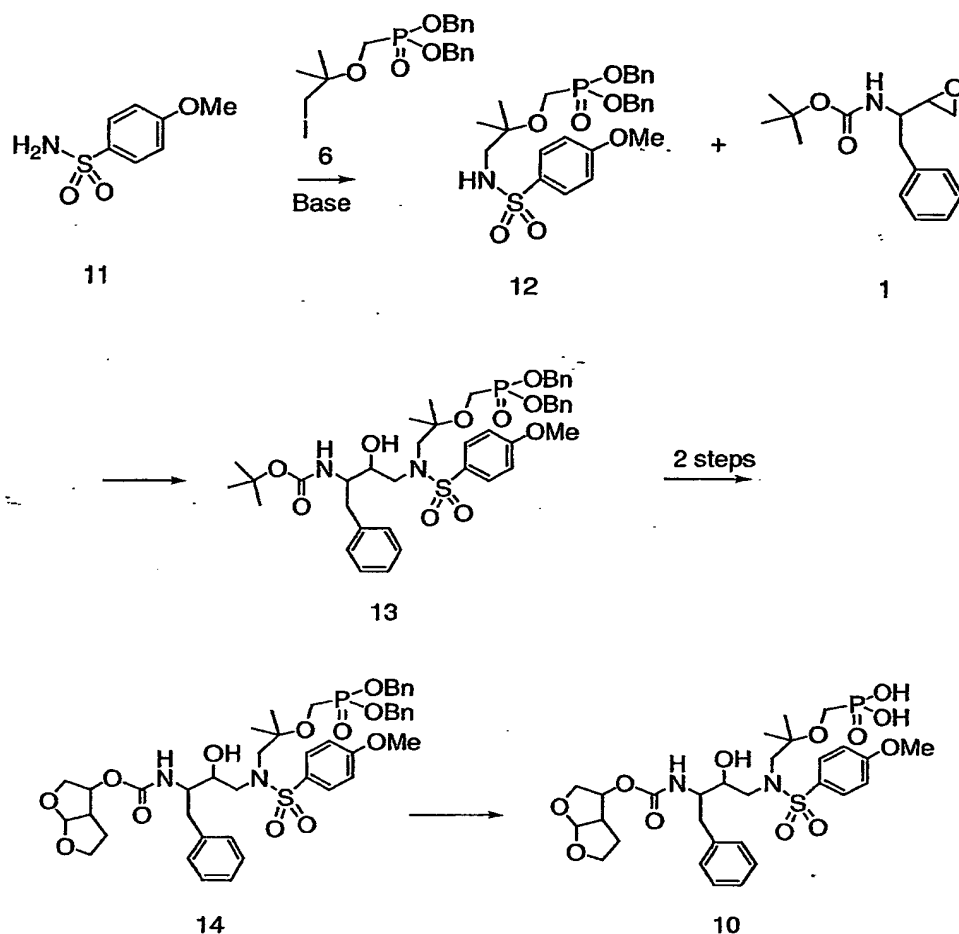
14   10

The sulfonamide 11 is readily alkylated with the iodide 6 (J. Med. Chem., 35, 2958, 1992) to
10 get the intermediate 12. Regioselective epoxide opening (JP -9124630) of the epoxide 1 with
    12 furnishes the intermediate 13. Deprotection of the BOC group followed by the treatment
    of bisfuranyl carbonate 8 yields the intermediate 14 which is subjected to hydrogenation to
    furnish the compound 10.

Scheme 103

1   15

16   13
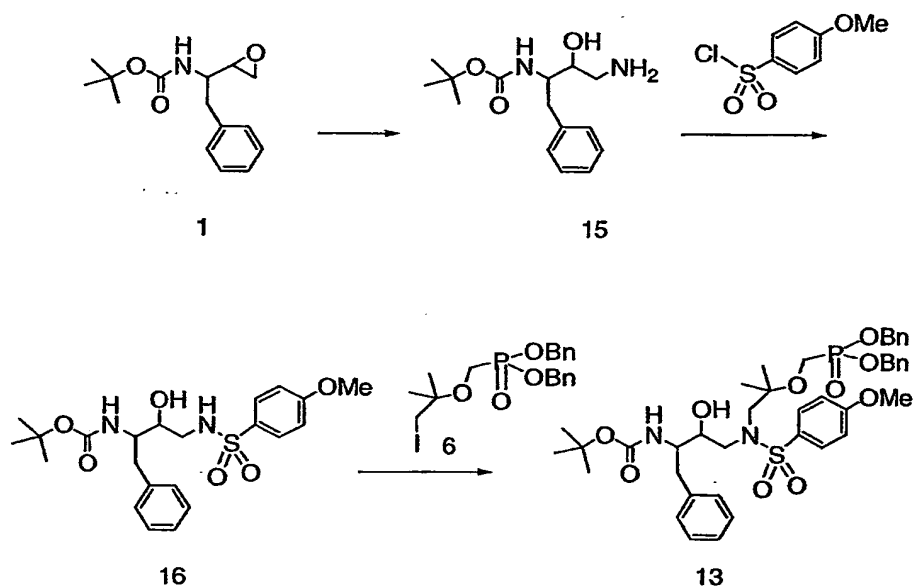
5   The epoxide 1 is converted to the aminohydroxyl derivative 15 using the known procedure (J. Med. Chem., 37, 1758, 1994). Sulfonylation of 15 using benzene sulfonylchloride affords the compound 16. Installation of the side chain to get the intermediate 13 is achieved by alkylation of sulfonamide nitrogen with iodide 6. The intermediate 13 is converted to the compound 10 using the same sequence as shown in scheme 102.
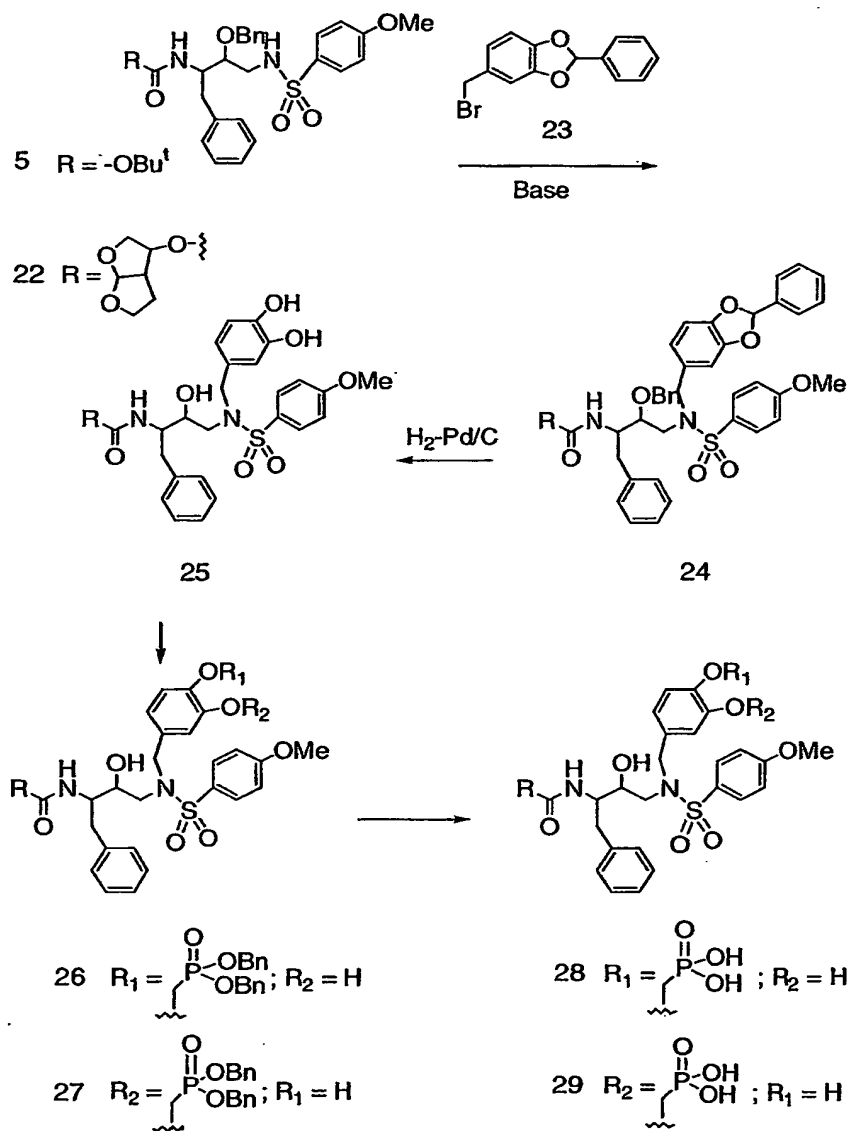
Scheme 104
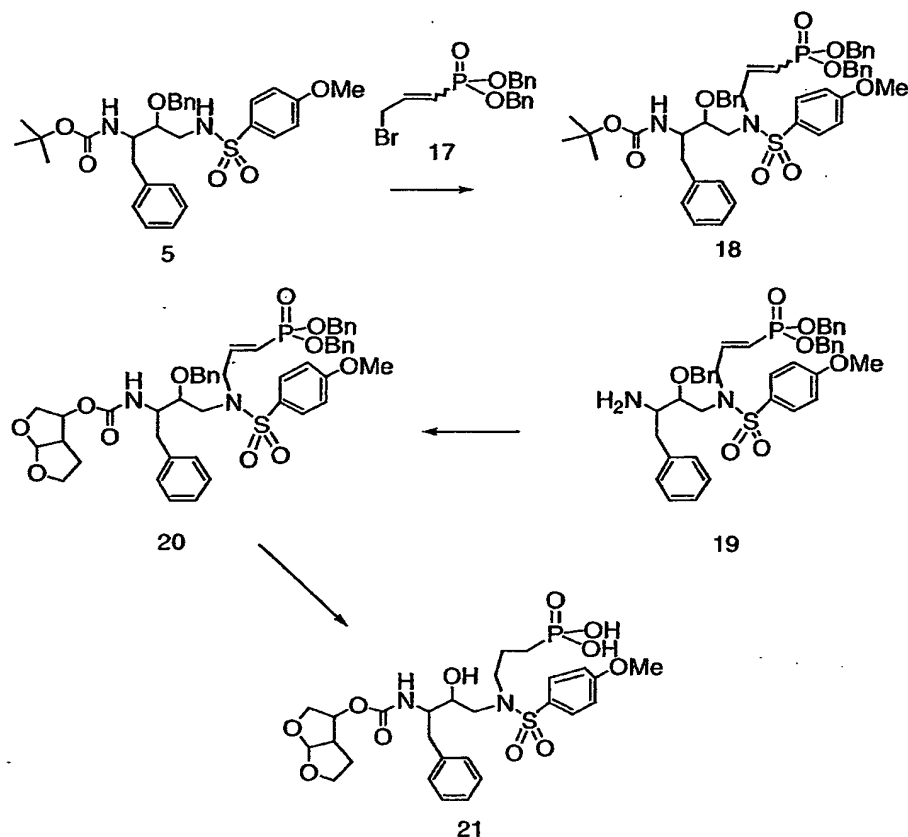
5

Sulfonamide 5 is alkylated under basic conditions using the allyl bromide 17 (Chem. Pharm. Bull., 30, 111, 1982) to get the intermediate 18. Similar transformation is reported in literature (J. Med. Chem., 40, 2525, 1997). Hydrolysis of BOC group with TFA and acylation of the resulting amine 19 with bisfuranyl carbonate 8 yields the compound 20.
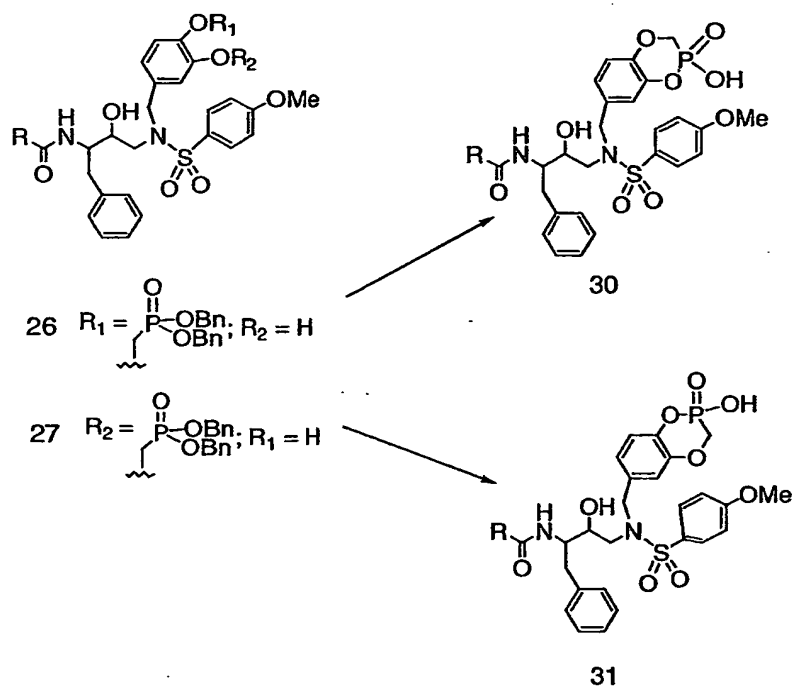
10   Hydrogenation using Pd/C catalysis under H$_2$ atmosphere affords the phosphonic acid 21.
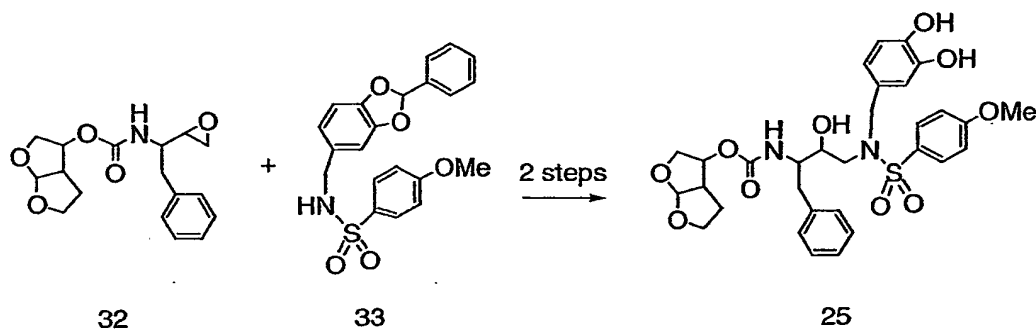
Scheme 105

5   R = -OBu^t

22 R =

25

H$_2$-Pd/C

24

26 R$_1$ = ; R$_2$ = H

27 R$_2$ = ; R$_1$ = H

28 R$_1$ = ; R$_2$ = H

29 R$_2$ = ; R$_1$ = H

5.

Scheme 105 (cont)

26 $R_1 = \underset{\|}{\overset{O}{P}}-\underset{OBn}{\overset{OBn}{}}; R_2 = H$

27 $R_2 = \underset{\|}{\overset{O}{P}}-\underset{OBn}{\overset{OBn}{}}; R_1 = H$

30

31

5   Sulfonamide 5 is converted to 22 via hydrolysis of BOC group with TFA and acylation with bisfuranyl carbonate 8. The sulfonamide 22 is alkylated with the bromide 23 (J. Med. Chem., 40, 2525, 1997) to get the compound 24, which upon hydrogenolysis gives the catechol 25. Alkylation of the phenolic groups using dibenzylhydroxymethyl phosphonate (J. Org. Chem., 53, 3457, 1988) affords regioisomeric compounds 26 and 27. These compounds 26 and 27

10   are hydrogenated to get the phophonic acids 28 and 29, respectively. Individual cyclic phosphonic acids 30 and 31 are obtained under basic (like NaH) conditions (US 5886179) followed by hydrogenolysis of the dibenzyl ester derivatives 26 and 27.
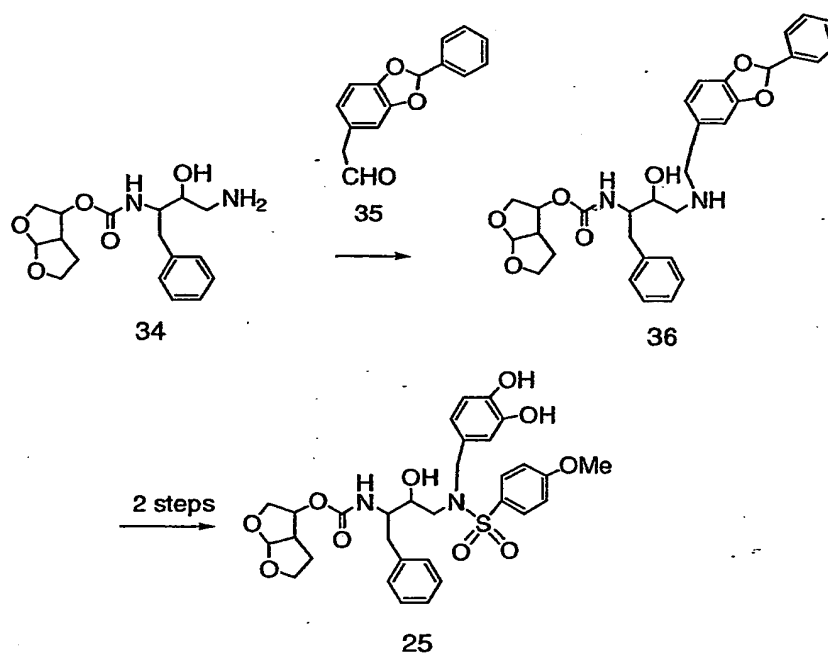
Scheme 106

In this route, compound 25 is obtained by conducting a reaction between the epoxide 32 and
5   the sulfonamide 33 using the conditions described in the Japanese Patent No. 9124630.
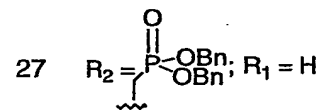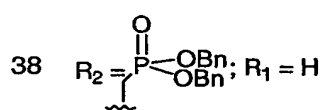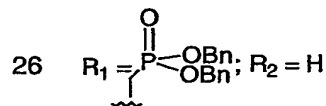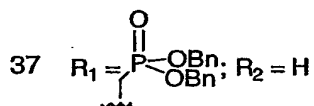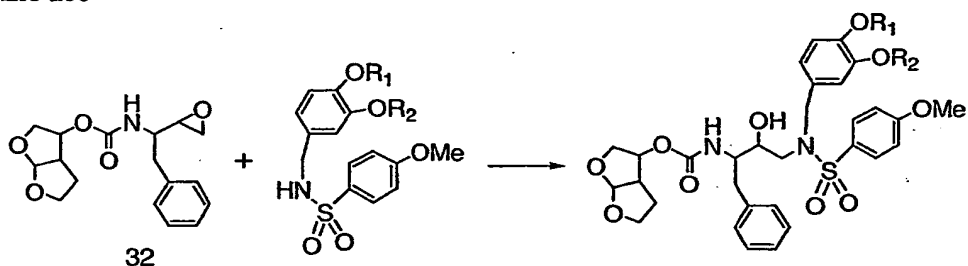

10   Epoxide 32 and sulfonamide 33 are synthesized utilizing similar methodology delineated in
the same patent.

Scheme 107

34 → 36

25

5   Compound 34 is obtained from 32 using similar sequence depicted in J. Med. Chem., 37,

1758, 1994. Reductive amination (for similar transformation see WO 00/47551) of

compound 34 with aldehyde 35 furnishes the intermediate 36 which is converted to the

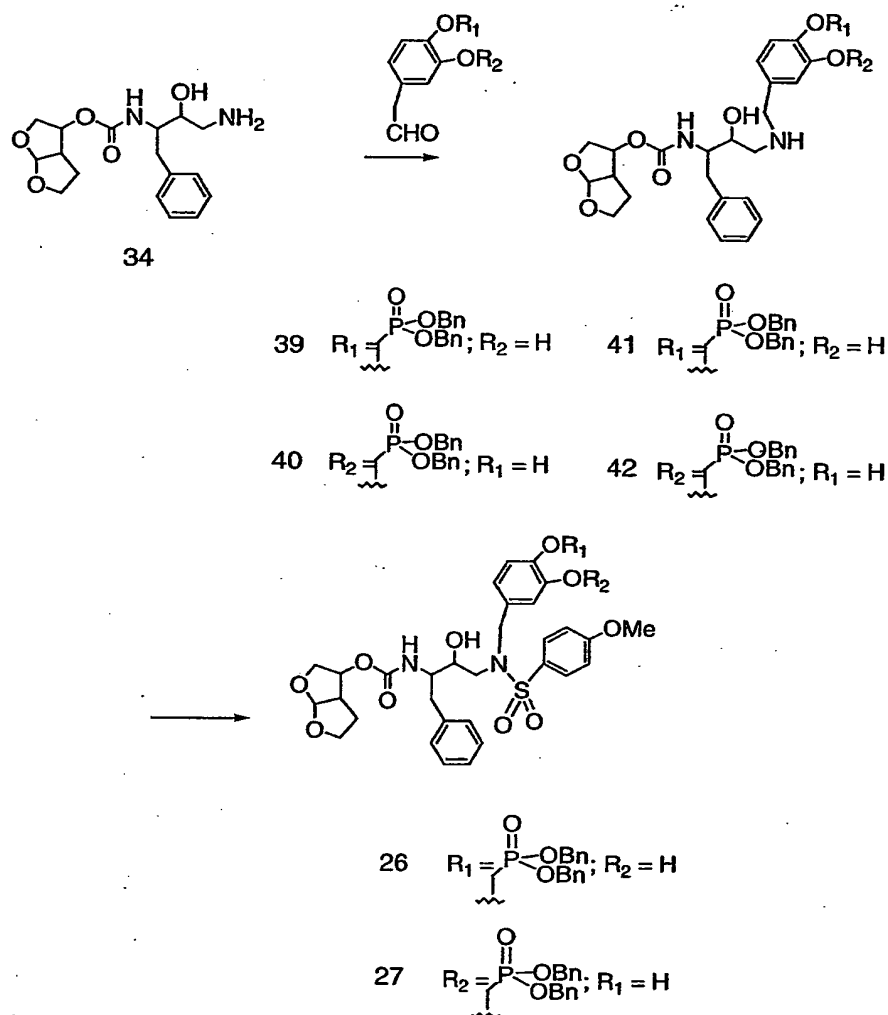compound 25 by sulfonylation followed by hydrogenation.

Scheme 108

| 37 | $R_1 = \overset{\overset{O}{\|}}{P}\overset{OBn}{\underset{OBn}{<}}$; $R_2 = H$ | 26 | $R_1 = \overset{\overset{O}{\|}}{P}\overset{OBn}{\underset{OBn}{<}}$; $R_2 = H$ |
| 38 | $R_2 = \overset{\overset{O}{\|}}{P}\overset{OBn}{\underset{OBn}{<}}$; $R_1 = H$ | 27 | $R_2 = \overset{\overset{O}{\|}}{P}\overset{OBn}{\underset{OBn}{<}}$; $R_1 = H$ |

5   Treatment of epoxide 32 with sulfonamides 37 and/or 38 under conditions described in
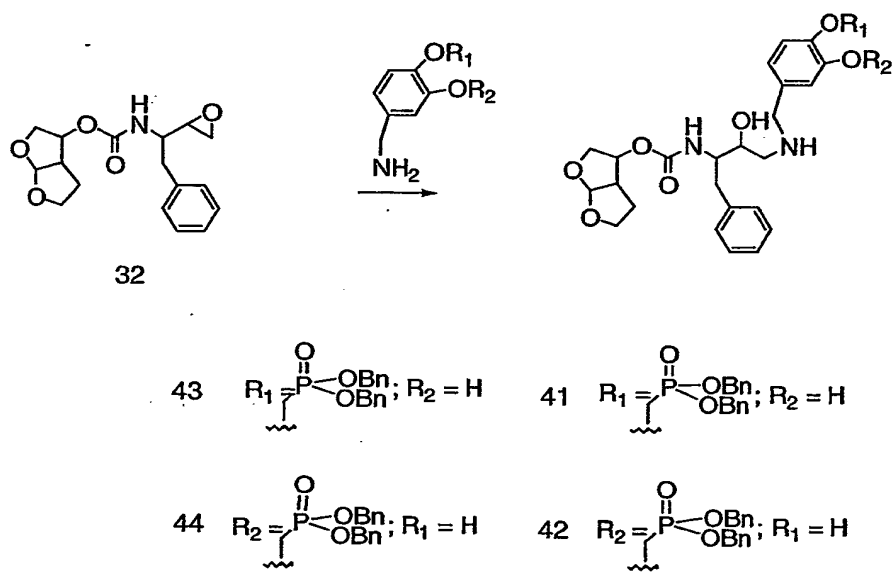Japanese Patent No. 9124630 furnishes 26 and 27.

Scheme 109

Reductive amination of aminohydroxyl intermediate 34 with the aldehydes 39 and 40 as
described in patent WO 00/47551, furnish 41 and 42 which undergoes smooth sulfonylation
to give 26 and 27.

39 $R_1 = $ (phosphonate with OBn, OBn); $R_2 = H$ 41 $R_1 = $ (phosphonate with OBn, OBn); $R_2 = H$

40 $R_2 = $ (phosphonate with OBn, OBn); $R_1 = H$ 42 $R_2 = $ (phosphonate with OBn, OBn); $R_1 = H$

26 $R_1 = $ (phosphonate with OBn, OBn); $R_2 = H$

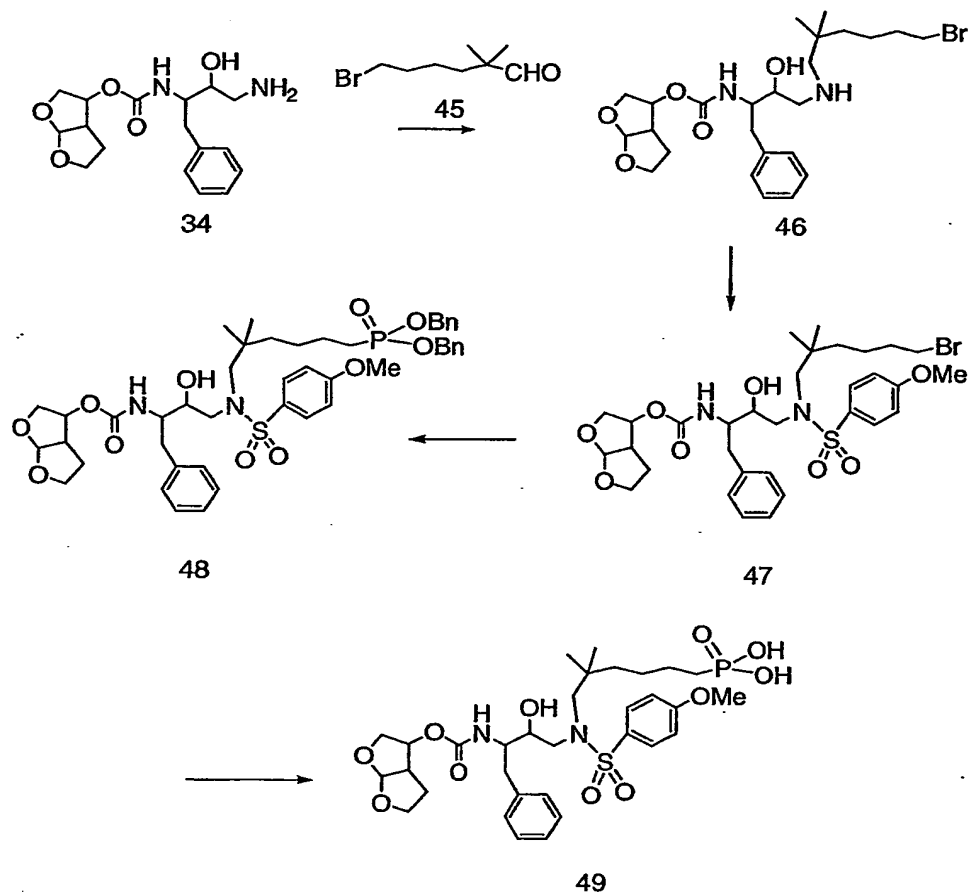27 $R_2 = $ (phosphonate with OBn, OBn); $R_1 = H$

Scheme 110

In an alternate approach, where epoxide 32 is opened with benzyl amines 43 and 44 under
conditions described above furnishes 41 and 42, respectively. Similar transformations were
documented in the Japanese Patent No. 9124630.

32

43   $R_1 = \overset{O}{\underset{\|}{P}}\overset{OBn}{\underset{OBn}{<}}$; $R_2 = H$ 41 $R_1 = \overset{O}{\underset{\|}{P}}\overset{OBn}{\underset{OBn}{<}}$; $R_2 = H$

44   $R_2 = \overset{O}{\underset{\|}{P}}\overset{OBn}{\underset{OBn}{<}}$; $R_1 = H$ 42 $R_2 = \overset{O}{\underset{\|}{P}}\overset{OBn}{\underset{OBn}{<}}$; $R_1 = H$
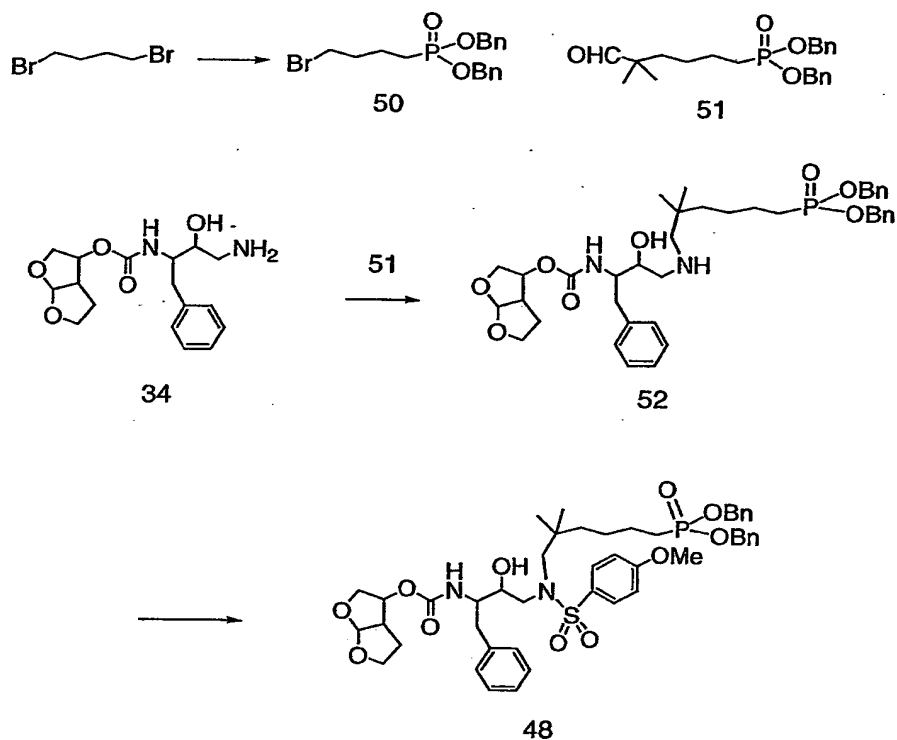
Scheme 111

34

45

46

48

47

49

5

Reductive amination of the bromoaldehyde 45 (J. Organomet. Chem., FR; 122, 123, 1976) with the amine 34 gives 46 which then undergoes sulfonylation to furnish 47. The bromoderivative 47 is converted to the phosphonate 48 under Michaelis-Arbuzov reaction

10 conditions (Bioorg. Med. Chem. Lett., 9, 3069, 1999). Final hydrogenation of 48 delivers the phosphonic acid 49.
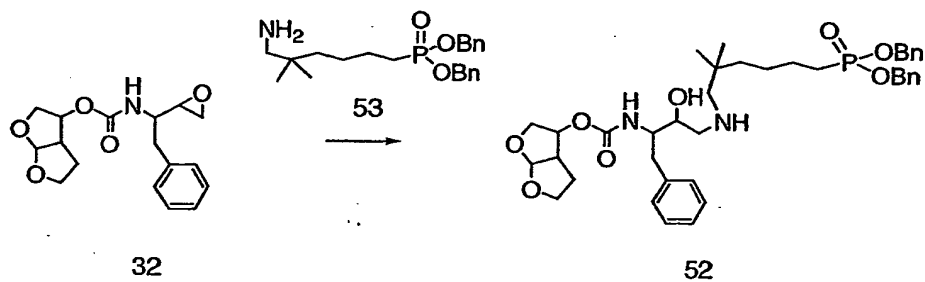
Scheme 112

The intermediate 48 is also obtained as shown in scheme 112. Reductive amination of the aldehyde 52 with the amine 34 offers the phosphonate 52 and sulfonylation of this intermediate furnishes 48.
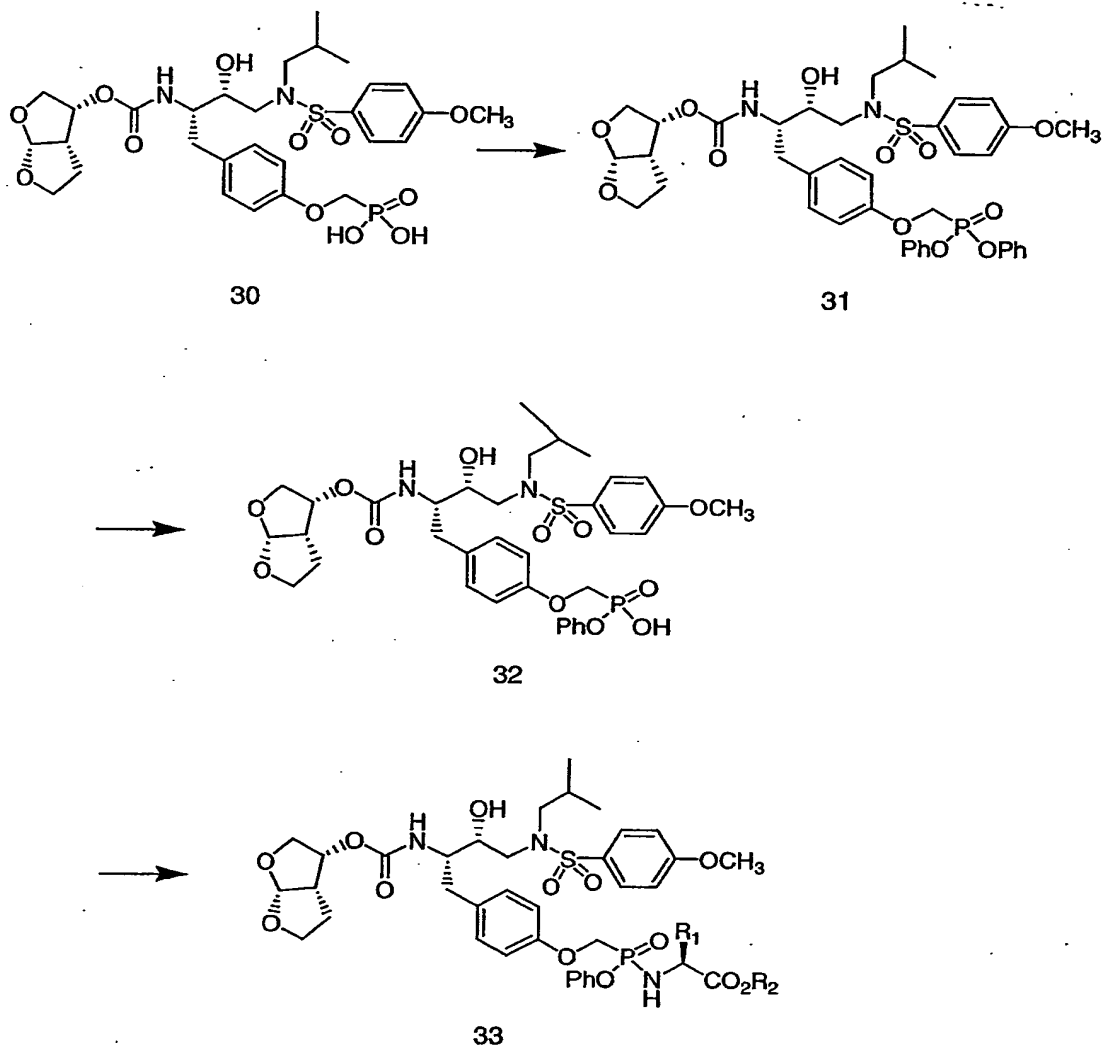
Scheme 113

5   32   52

Alternatively, compound 52 is obtained from the epoxide 32 by a ring opening reaction with

10   the aminophosphonate 53 (Scheme 113).
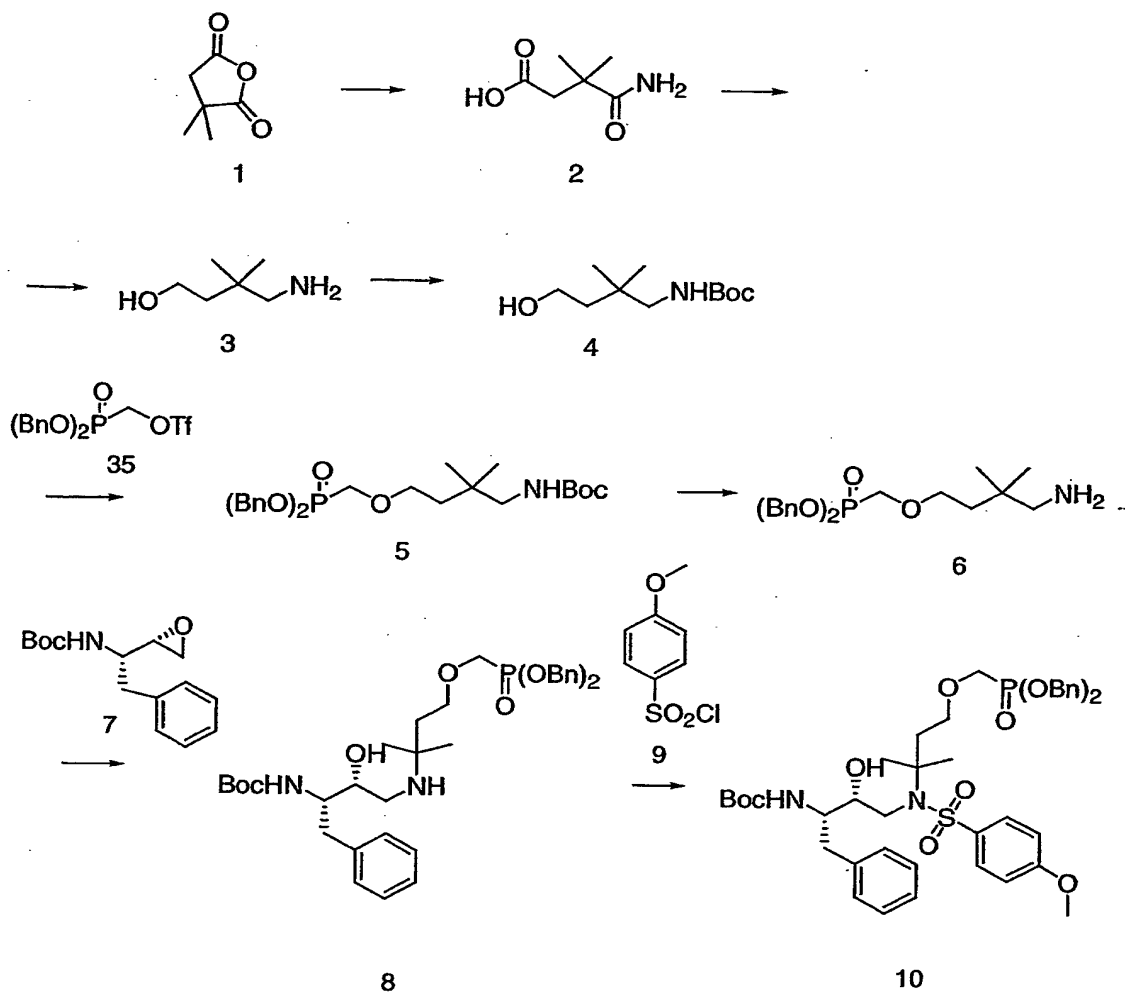
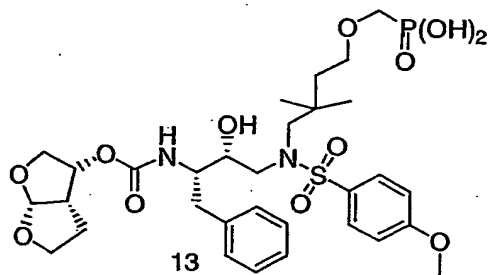## Scheme Section C
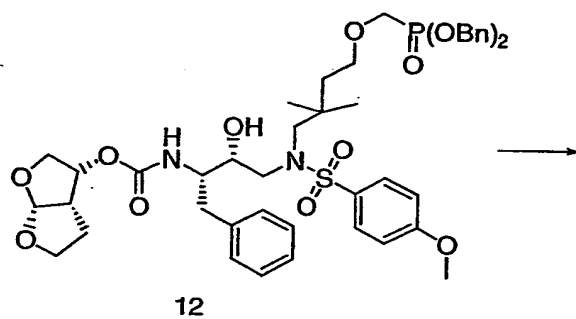
Scheme 9 is described in the Examples.
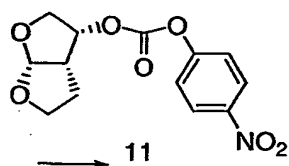
5   **Scheme 9**

30

31

32

33

Scheme Section D

The following schemes are described in the Examples.

11

12

13

-1200-

28

29

30

31

32

34

CH₃SO₃H
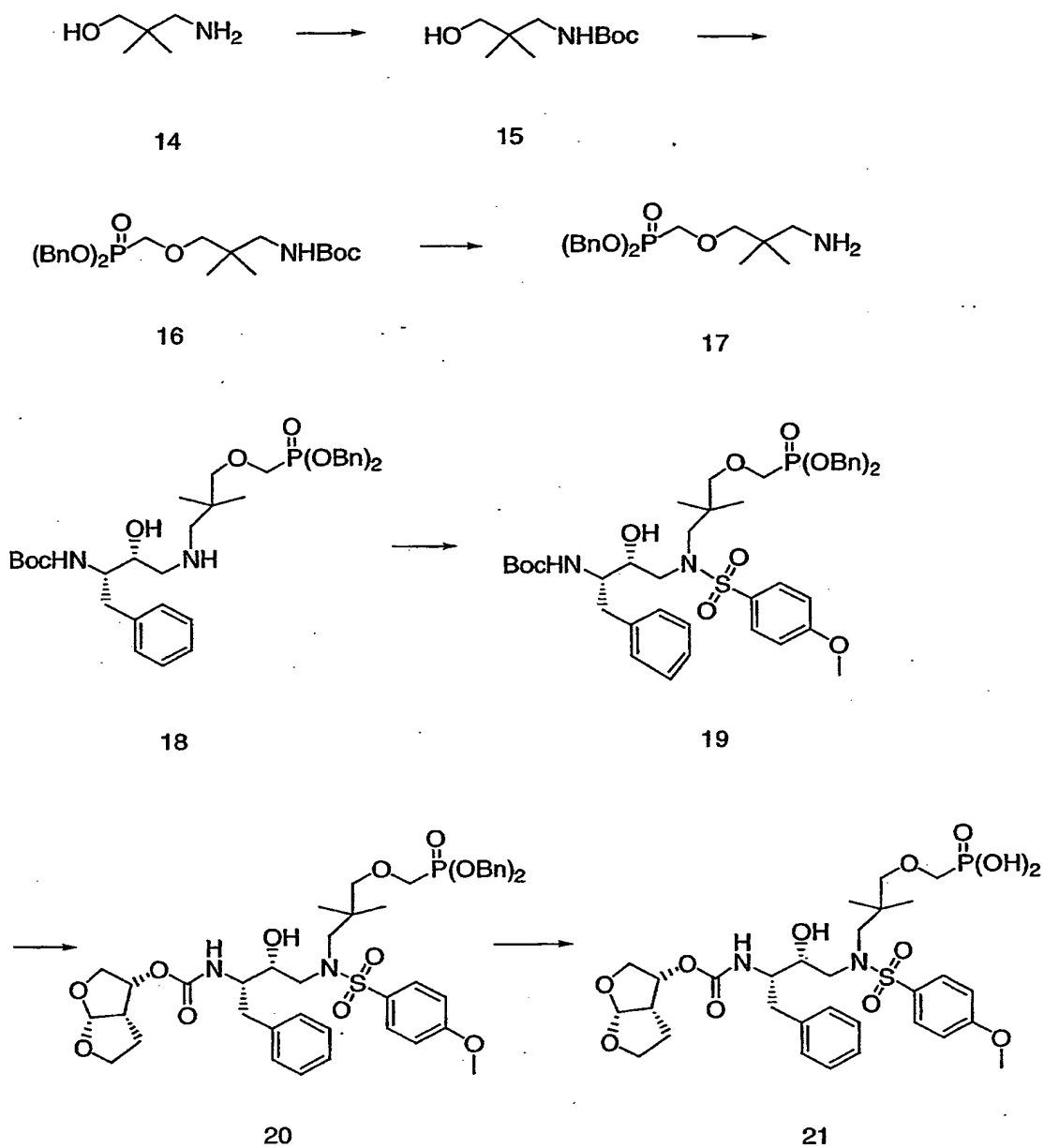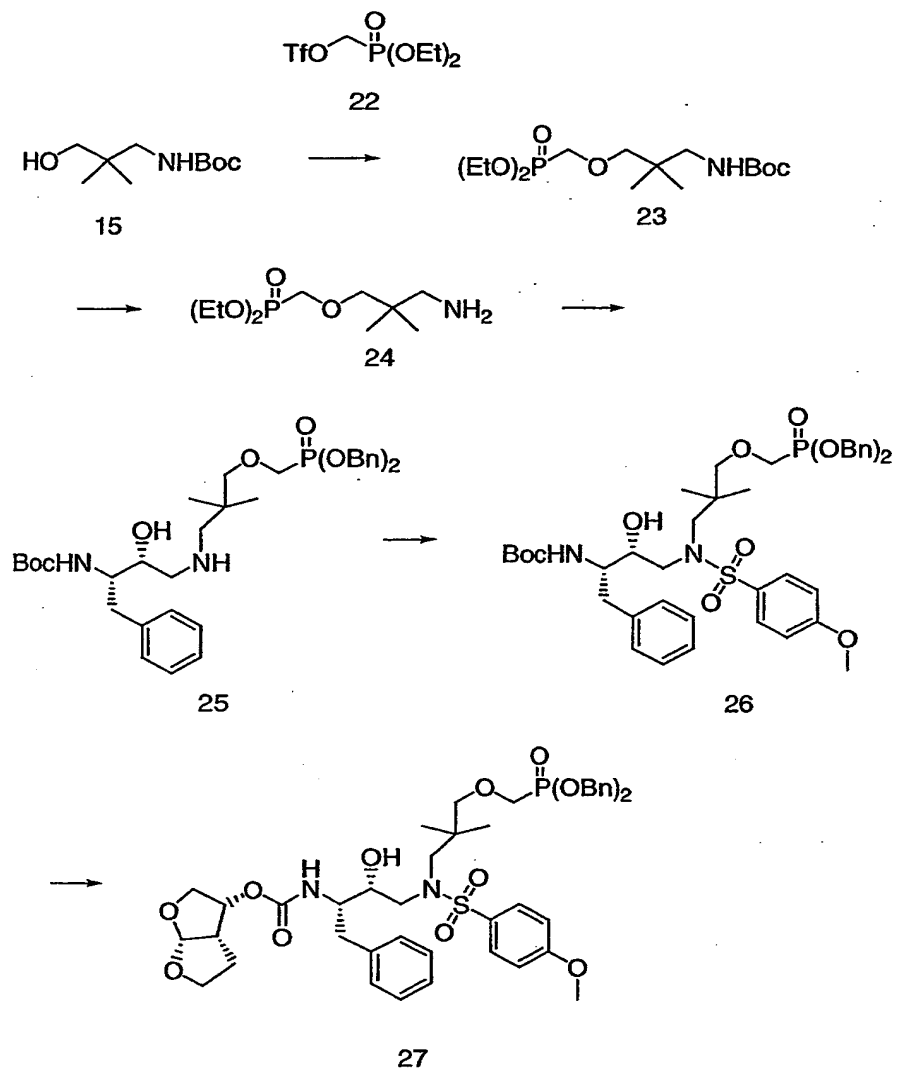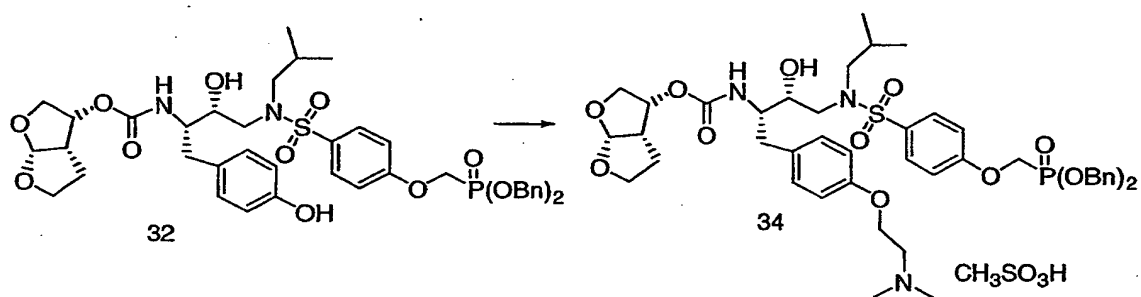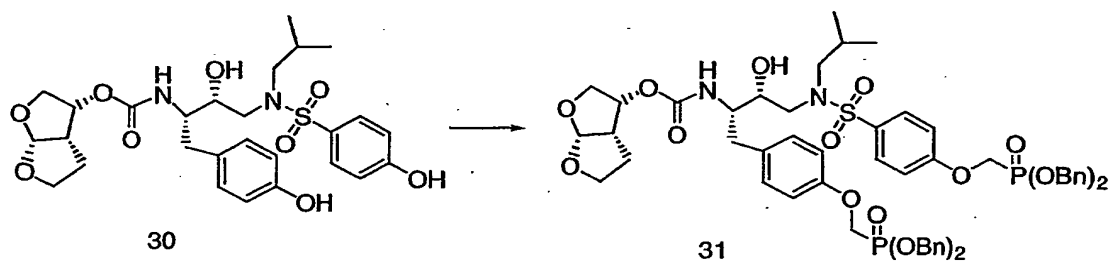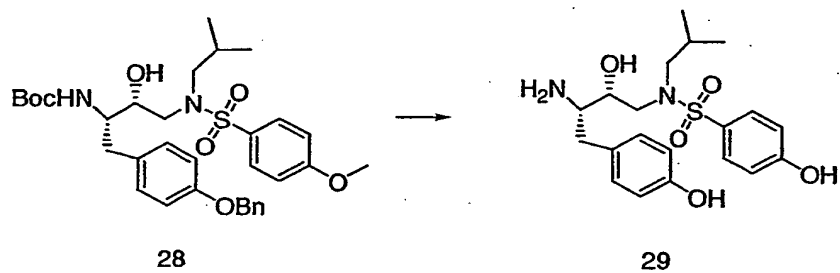
Scheme Section E

Schemes 1-3 are described in the examples.

Scheme 1

5
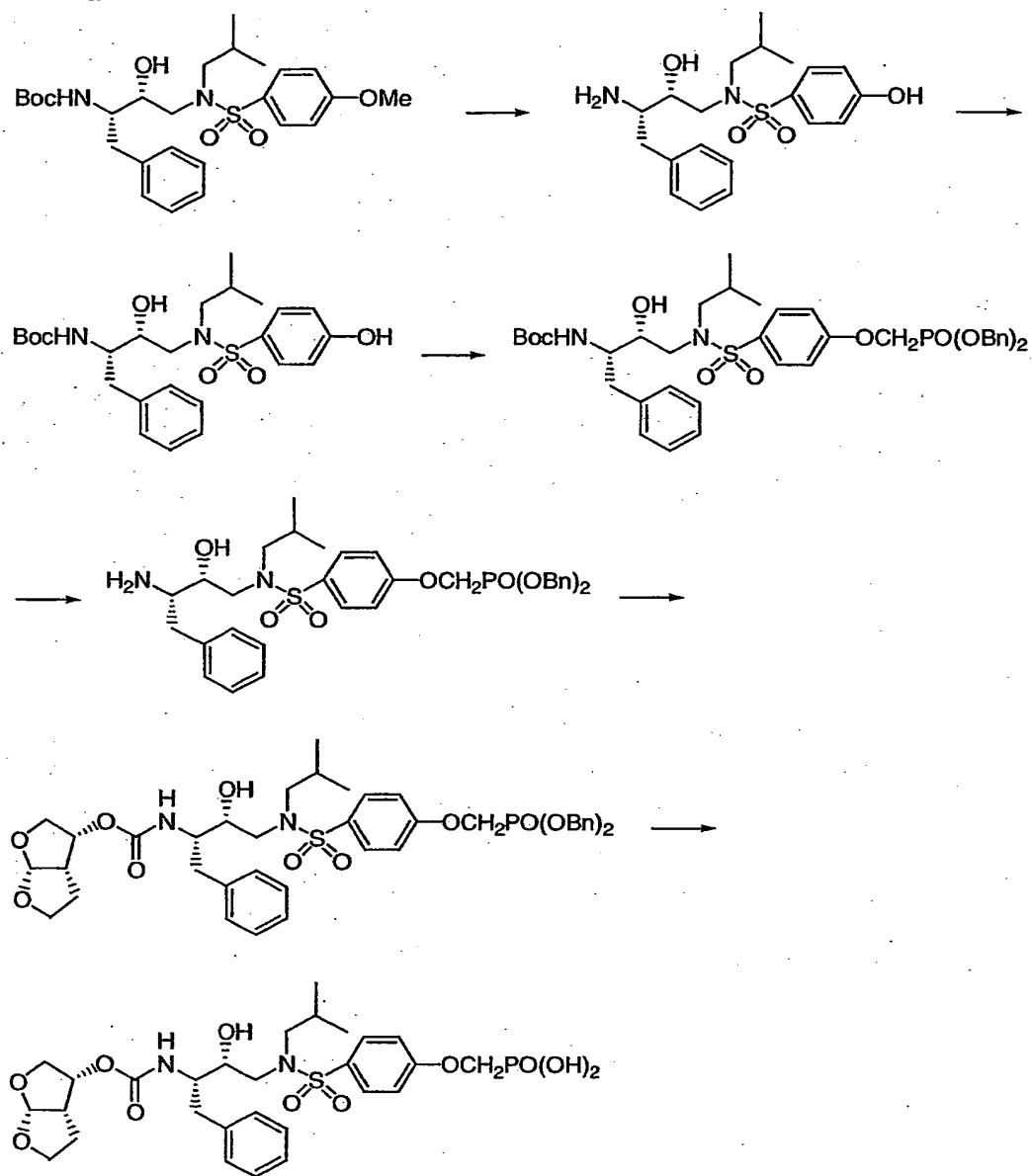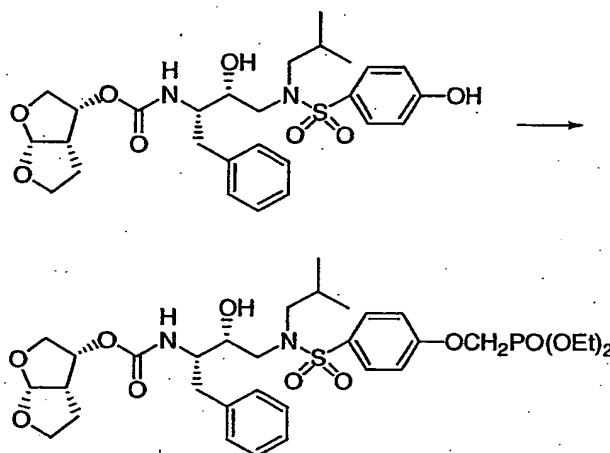
Scheme 2

5
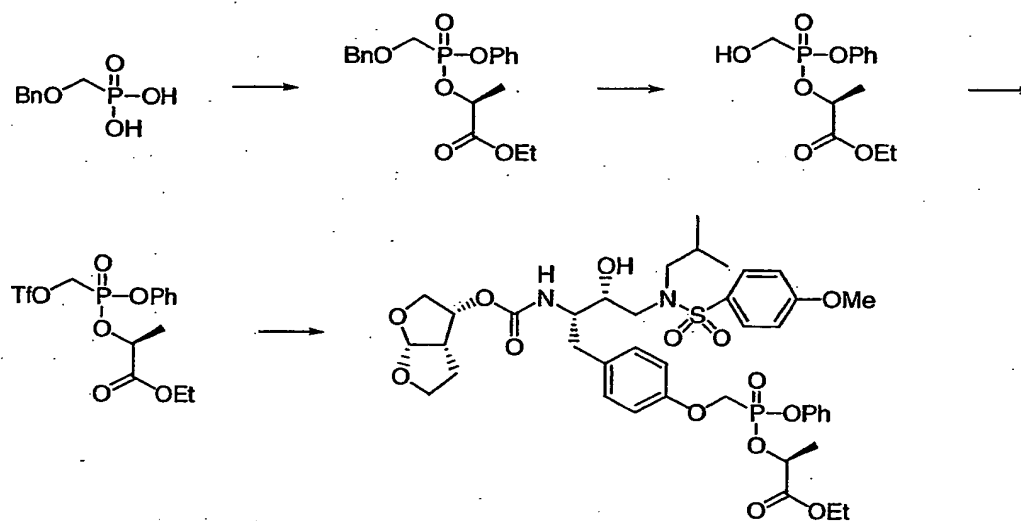
Scheme 3

Scheme Section F

Schemes 1-5 are described in the examples.

Scheme 1

1

2

3

4

5

6

Scheme 2

2   7   8

9   10

Scheme 3

2

11

12

13

14

Scheme 4

15

16

17

18

19

5

-1208-

Scheme 5

17

20

21
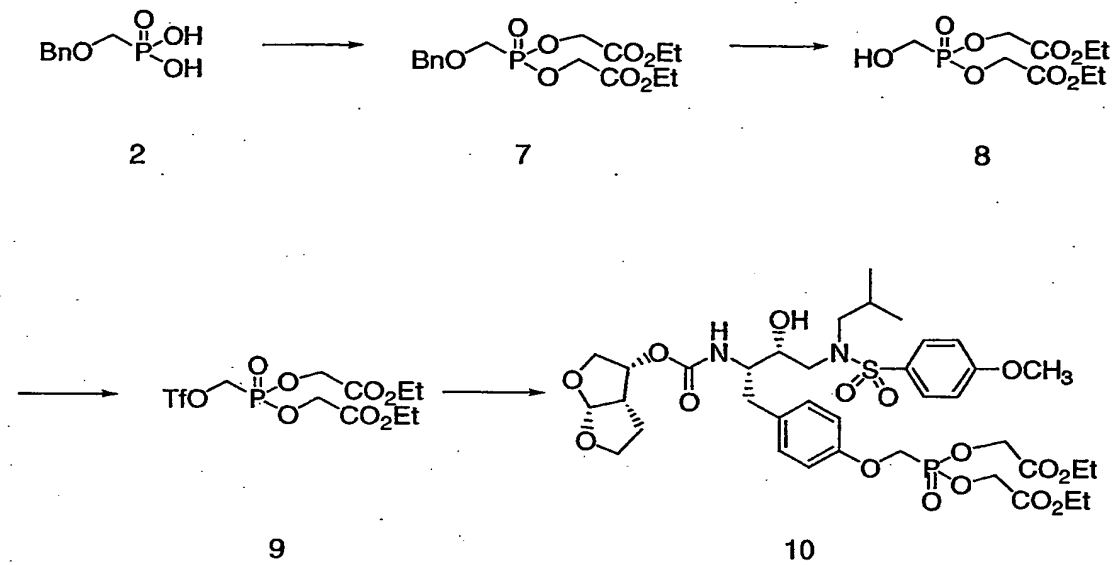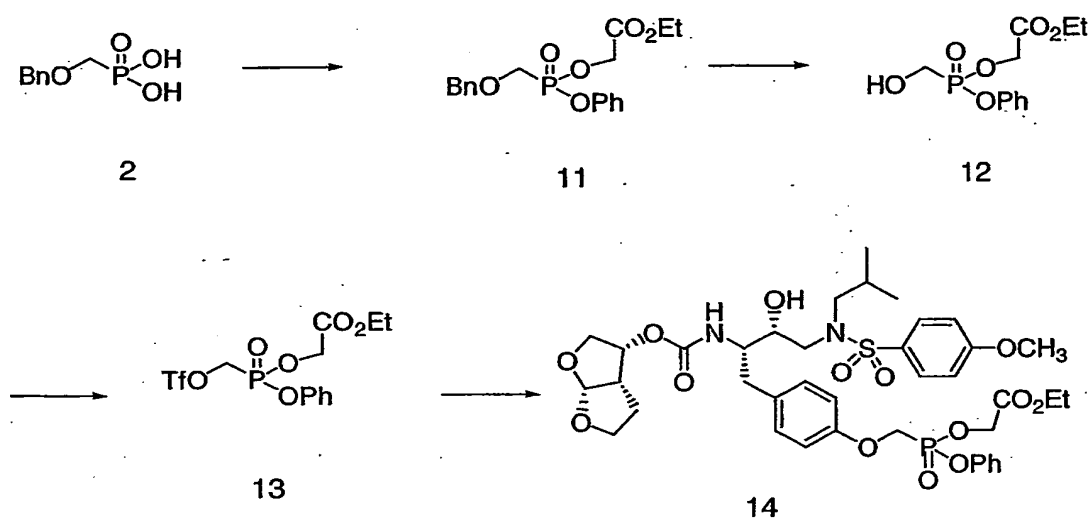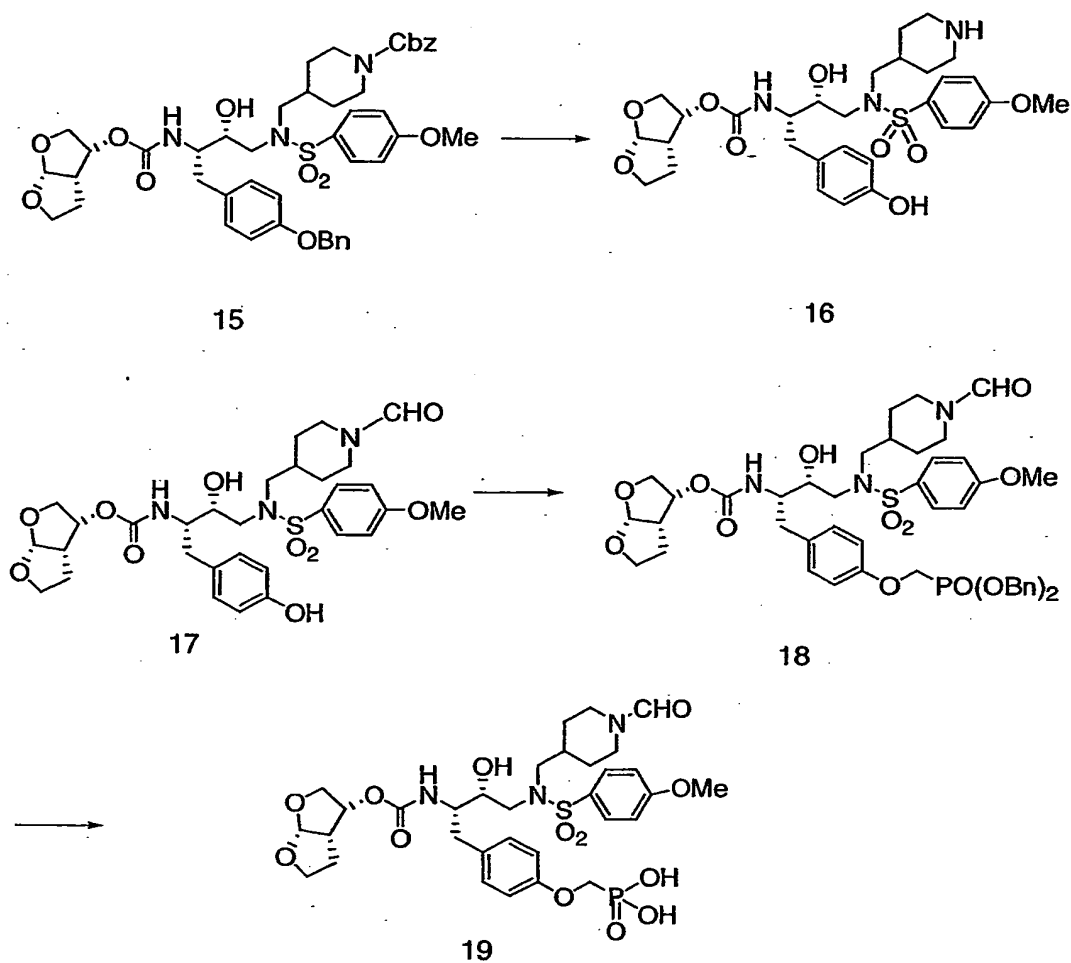
Scheme Section G

Schemes 1 to 9 are described in the examples.
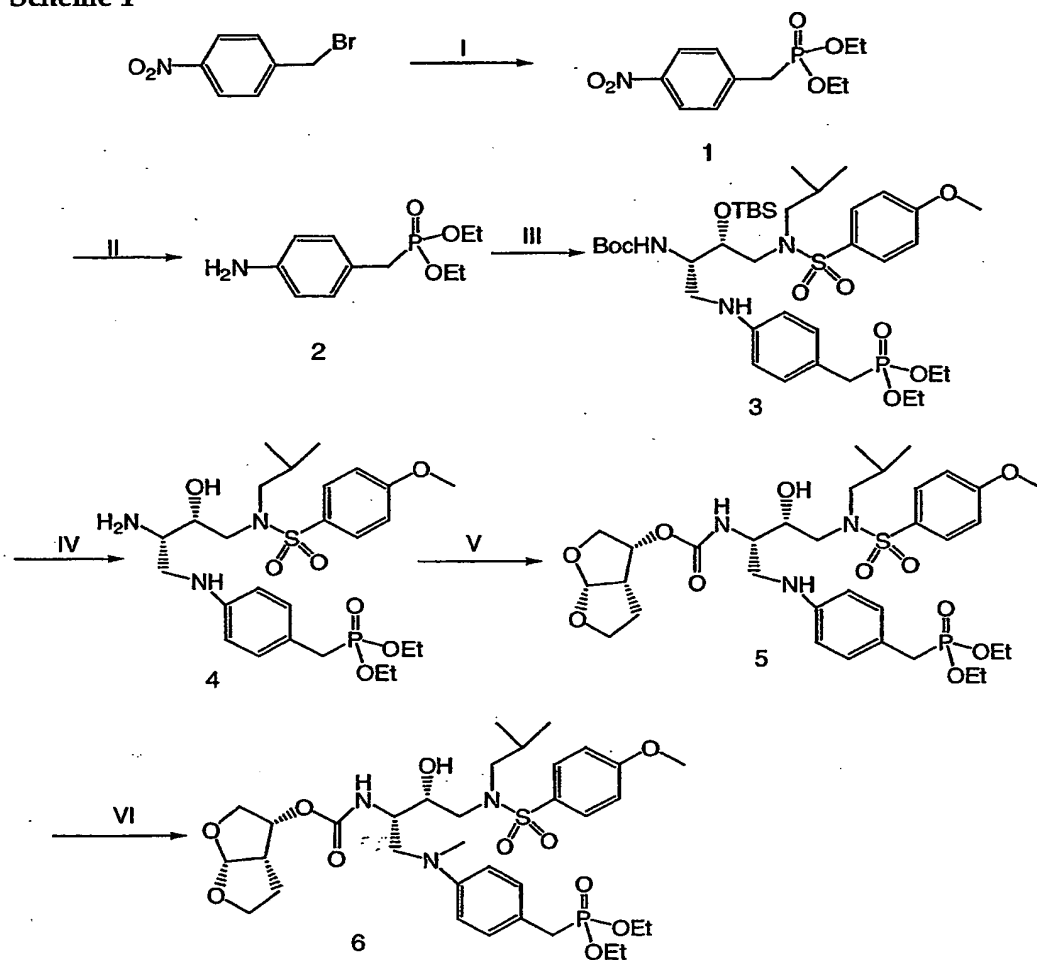
Scheme 1

I. P(OEt)$_3$/120 C; II. H$_2$/10%Pd-C; III. See Scheme Section H, Scheme 13, Compound 48 /NaBH$_3$CN/HOAc/MeOH; IV. a. TFA; b. n-Bu$_4$NF;V. bisfurancarbonate/DMAP; VI. HCHO/NaBH$_3$CN/HOAc/MeOH

5
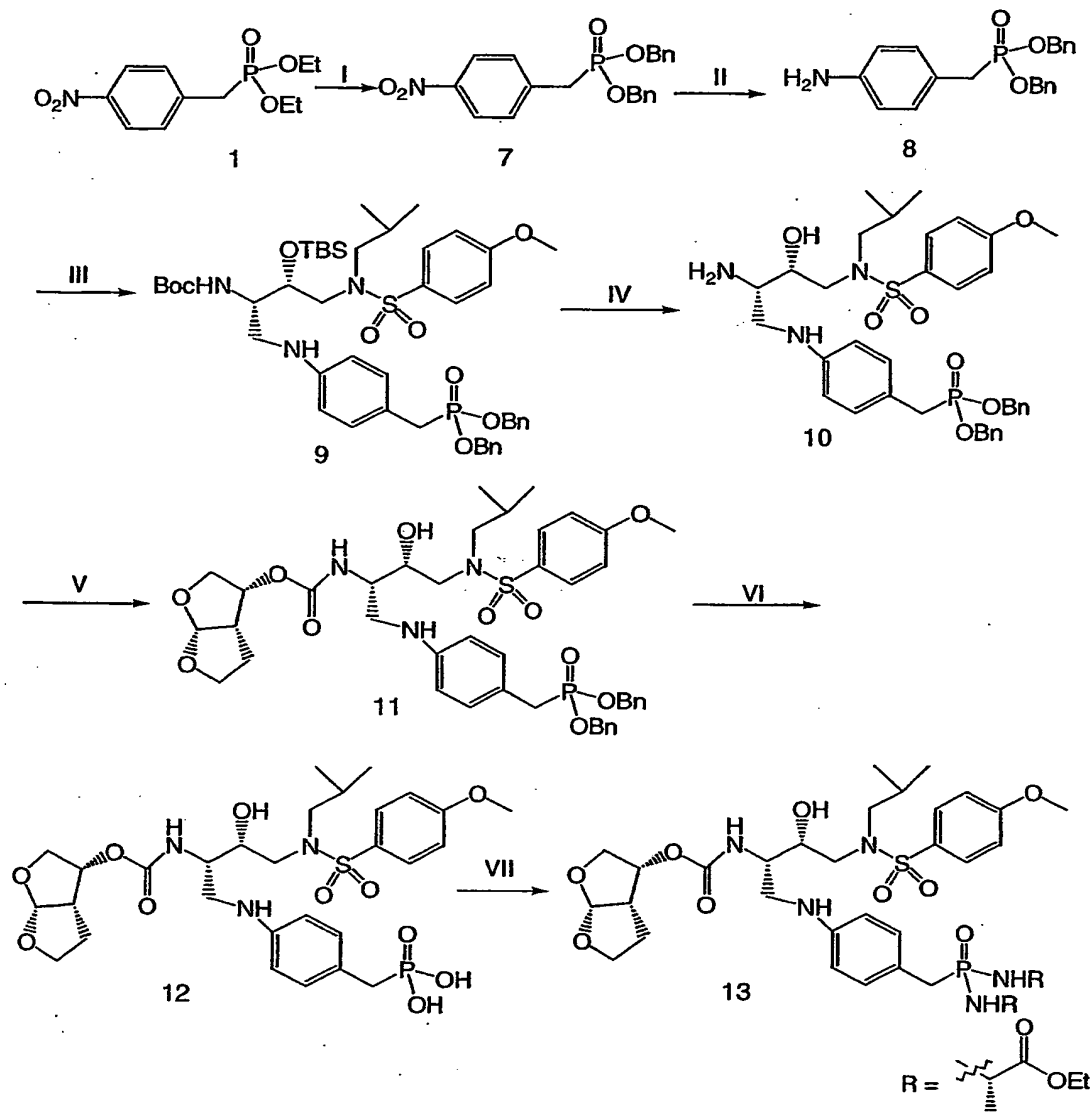
Scheme 2

I. a.TMSBr; b. SOCl₂/60 C; c. BnOH/Et₃N; II. Zn/HOAc; III. See Scheme Section H, Scheme 13, Compound 48 /NaBH₃CN/HOAc/MeOH; IV. a. TFA; b. n-Bu₄NF; V. bisfurancarbonate/DMAP; VI. H₂/10%Pd-C; VIII.RNH₂/PPh₃/aldrithiol

Scheme 3
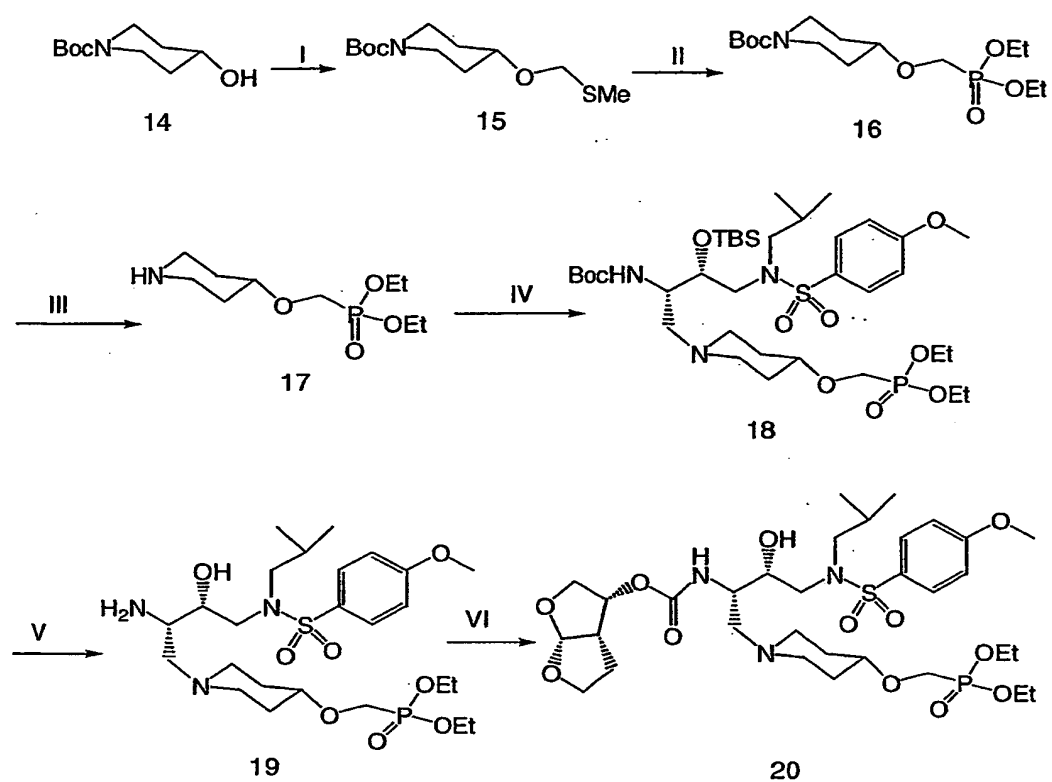
I. a. NaH; b. MTMCl; II. a. SOCl₂; b. P(OEt)₃/120 C; III. TFA; IV. See Scheme Section H, Scheme 13, Compound 48 /NaBH₃CN/HOAc/MeOH; V. a. TFA; b. n-Bu₄NF; VI. bisfurancarbonate/DMAP
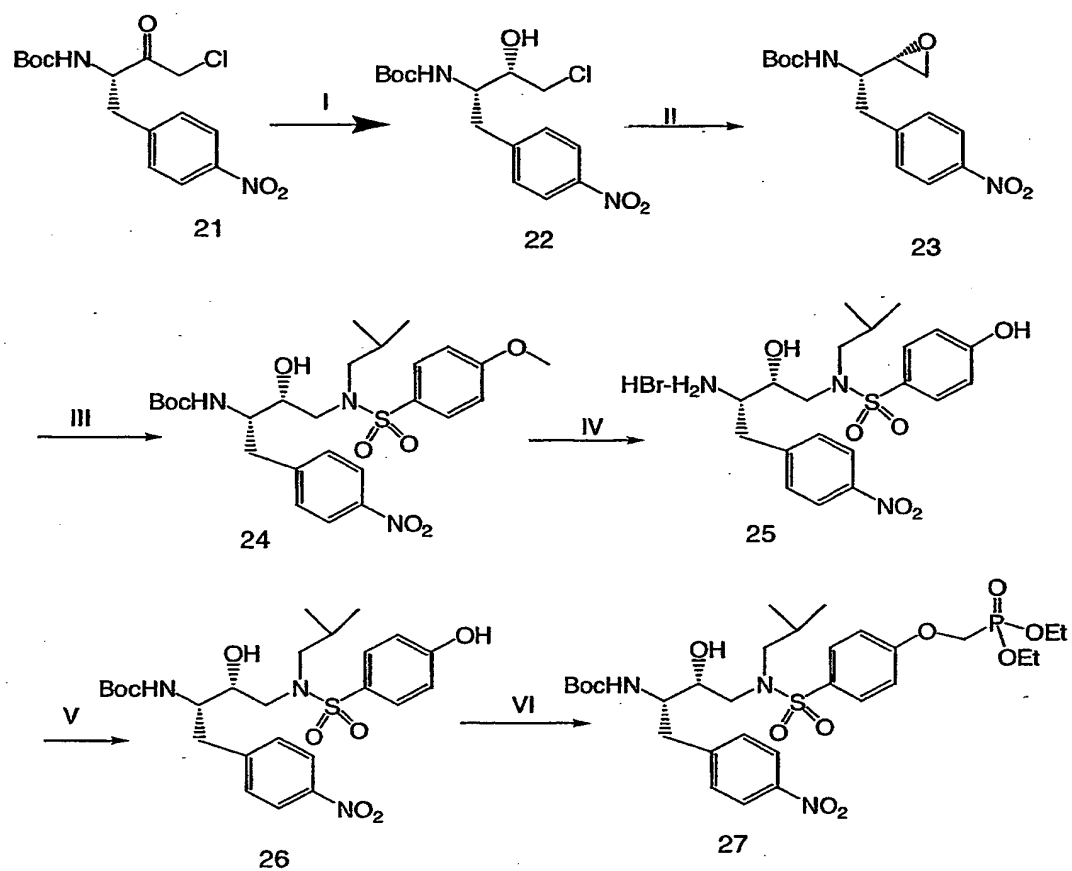
Scheme 4

I. NaBH$_4$/THF/H$_2$O ; II. KOH/EtOH; III. a. isobutylamine/iropropanol/80 C; b.
4-methoxybenzenesulfonyl chloride/Et$_3$N; IV.BBr$_3$/CH$_2$Cl$_2$; V. Boc$_2$O/NaHCO$_3$; VI.
TfOCH$_2$PO(OEt)$_2$/Cs$_2$CO$_3$

Scheme 5

27 $\longrightarrow$

28

$\longrightarrow$

29

$\longrightarrow$

30
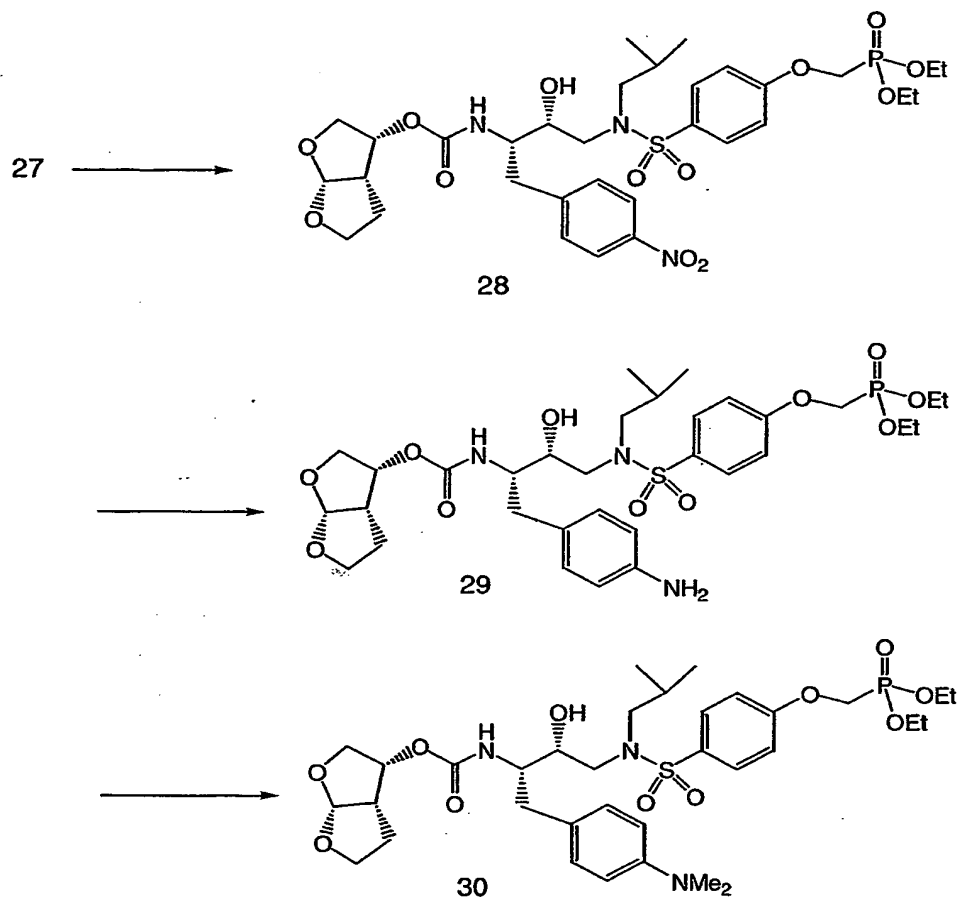
I. TFA/CH$_2$Cl$_2$; b. bisfurancarbonate/DMAP ; II. H$_2$/10% Pd-C/EtOH;
III. HCHO/NaBH$_3$CN/HOAc/MeOH

-1214-

Scheme 6

25   31

32

33
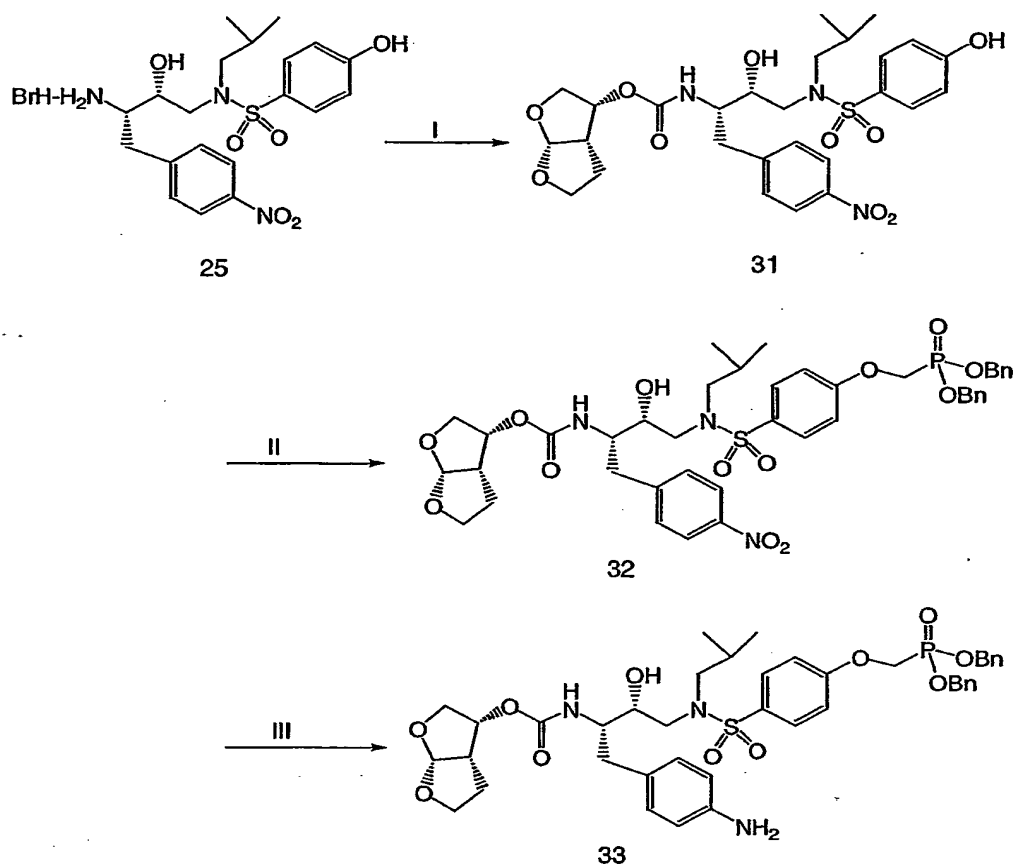
I.a. TMSCl/Et$_3$N; b. bisfurancarbonate/DMAP; c. n-Bu$_4$NF/HOAc; II.
TfOCH$_2$PO(OBn)$_2$/Cs$_2$CO$_3$; III. Zn/HOAc

Scheme 7

32 $\xrightarrow{\text{I}}$ **34**

$\xrightarrow{\text{II}}$ **35**

R =
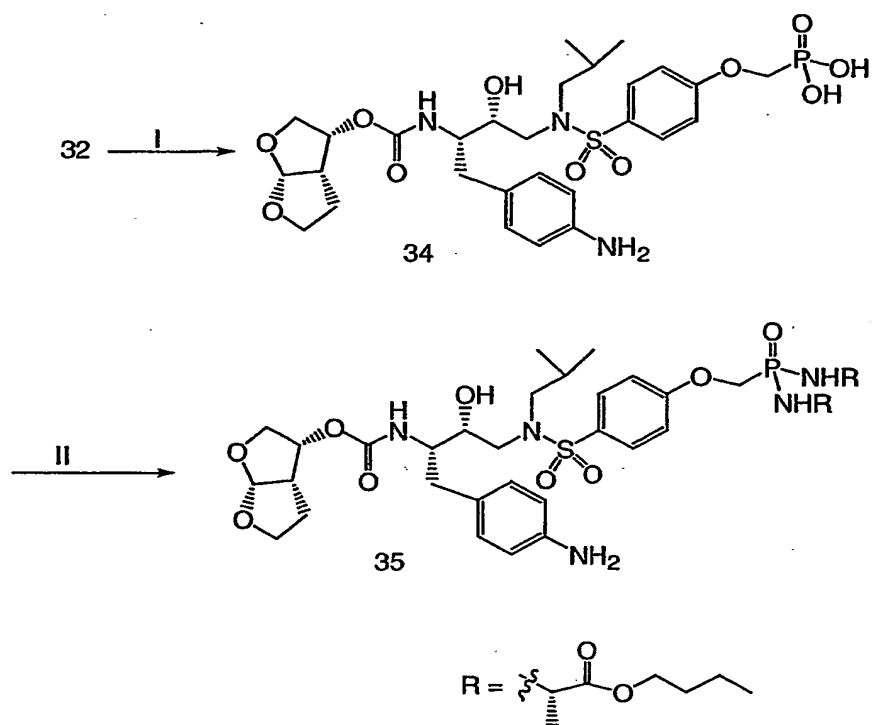
I. H$_2$/10% Pd-C; II. RNH$_2$/PPh$_3$/Aldrithiol/diisopropylethylamine/pyridine

Scheme 8

I. RNH₂/PPh₃/Aldrithiol/diisopropylethylamine/pyridine

37 R =

38 R =

39 R =
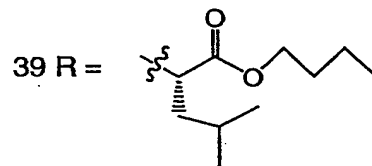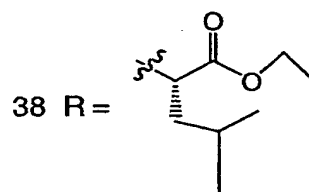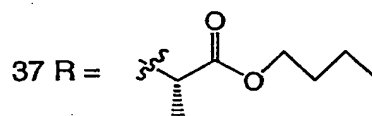
Scheme 9

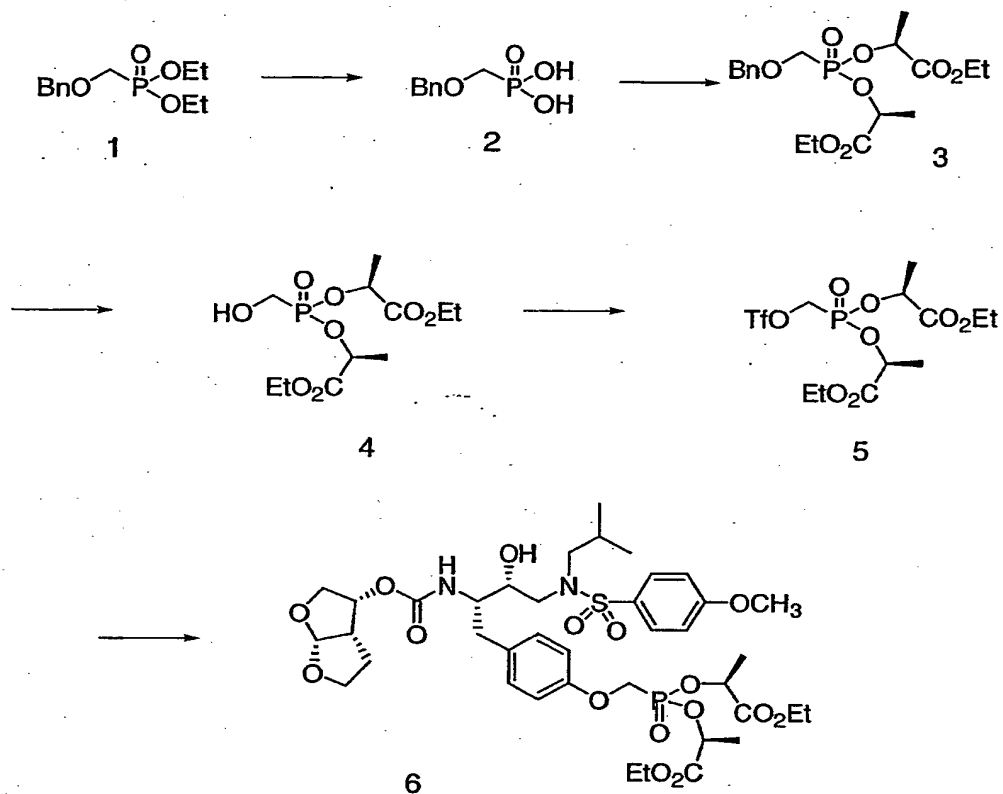I. RNH$_2$/PPh$_3$/Aldrithiol/diisopropylethylamine/
pyridine

41 R =

42 R =
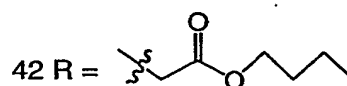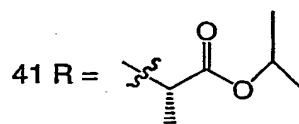
Scheme Section H

Schemes 1-14 are described in the examples.

Scheme 1

5

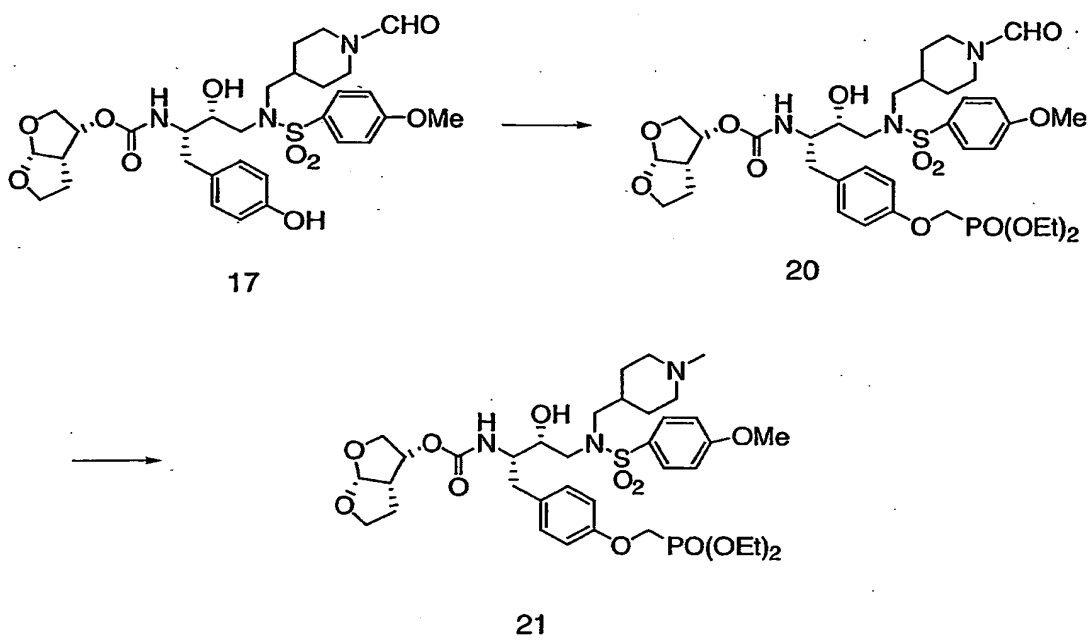**Scheme 2**

(1) BSA, CN₃CN, 70°C

(2) CBzCl, Py, 0°C to r.t.

7

DCC, PhOH

Py, 70°C

8

NaOH, CH₃CN

9

Scheme 3

HCl.H$_2$N CO$_2$/Pr
─────────────
DCC, Py, 70°C →

10

·Pd / C, H$_2$
─────────────
EtOAc →

11

12a-c
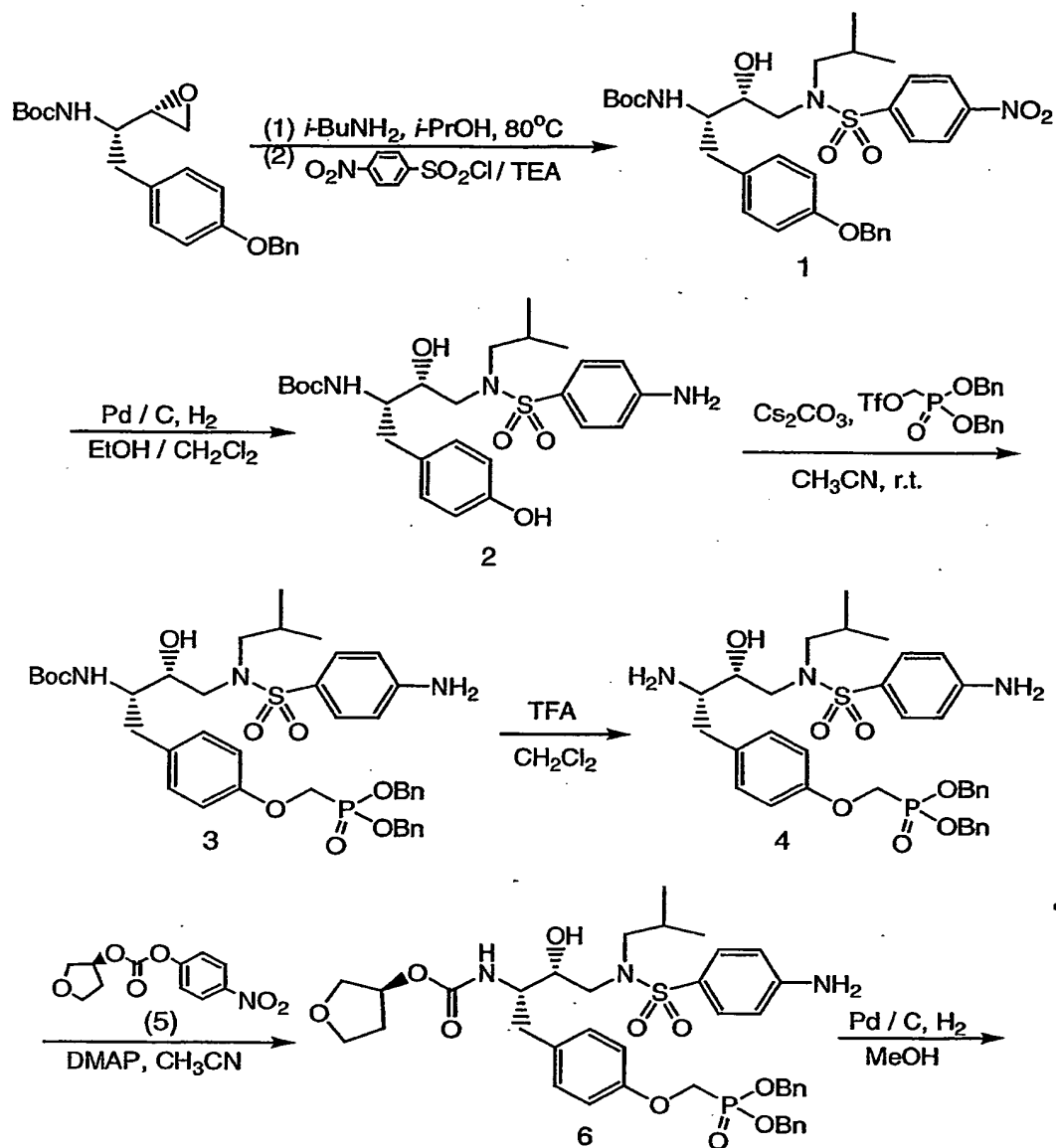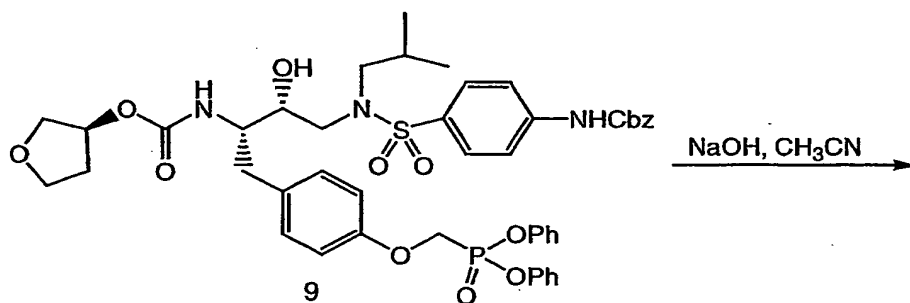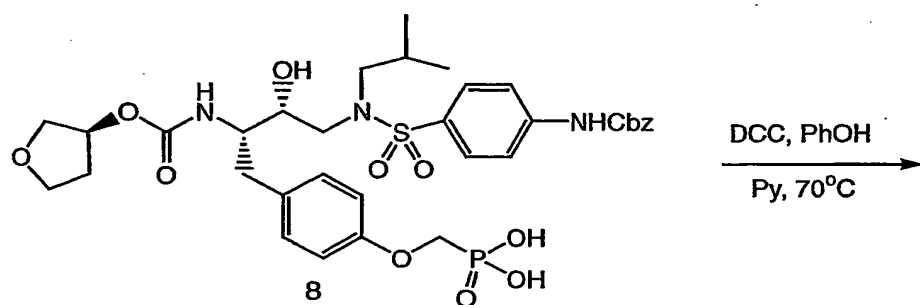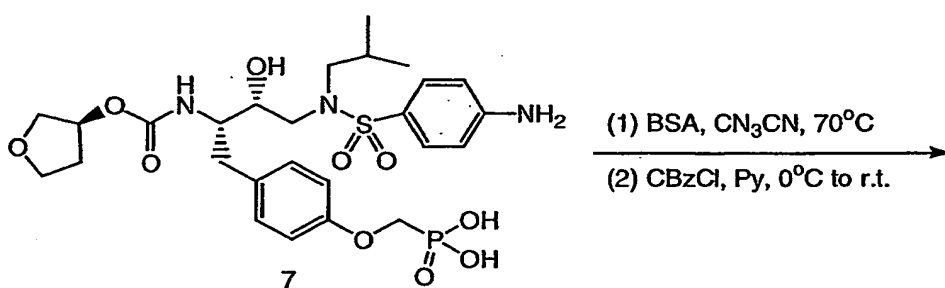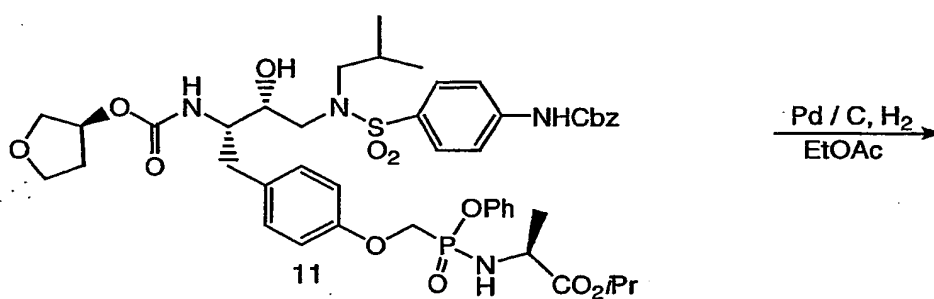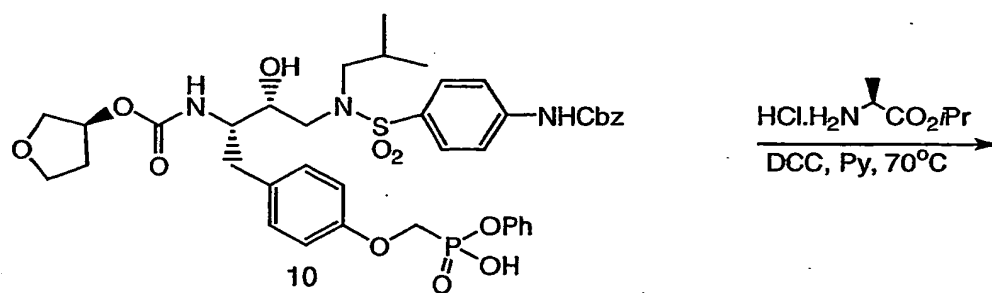
12a, GS 108577 (isomer A / B = 1 : 1)
12b, GS 108578 (isomer A)
12c, GS 108579 (isomer B)

Scheme 4

Scheme 5

16

17

Zn, HOAc

18

10% Pd / C, H₂

MeOH / HOAc

19
GS 17424

Scheme 6

(1) TMSCl, TEA, CH_2Cl_2
(2) Boc_2O, TEA, CH_2Cl_2

(3) 1.0 M TBAF / HOAc, THF

20

Cs_2CO_3, TfO$\frown$$\overset{O}{\underset{\underset{OBn}{\parallel}}{P}}\overset{OBn}{}$

THF, r.t.

21

TFA, CH_2Cl_2

22

DMAP, CH_3CN

23

Scheme 7

Compound **24**, reagents: Pd / C, H₂, EtOH

Compound **25**, reagents: (1) BSA, CN₃CN, 70°C (2) CBzCl, Py, 0°C to r.t.

Compound **26**, reagents: DCC, PhOH, Py, 70°C

Compound **27**, reagents: NaOH, CH₃CN

Scheme 8

28

HCl.H₂N—CO₂iPr

DCC, Py, 70°C

29

Pd / C, H₂

EtOH

30 a-b

30a R = H, GS 77369
30b R = Et, GS 77425

Scheme 9

31

32
GS 17389

Scheme 10

33

Reagents: NTf$_2$, Cs$_2$CO$_3$ / THF / CH$_2$Cl$_2$

34

Reagents: Pd(OAc)$_2$, CO, dppp / Et$_3$SiH, TEA, DMF

35

Reagents: NaBH$_4$ / THF / H$_2$O (9 / 1)

Scheme 11

36

(1) MsCl, TEA
    THF / CH₂Cl₂

(2) LiBr, 45 min

37

P(OEt)₃, toluene

120°C, overnight

38

GS 191338

Scheme 12

-1230-

Scheme 13

43 + (1) isobutylamine / (2) MeO—C₆H₄—SO₂Cl / TEA → 45

45 → (TBSOTf / TEA, CH₂Cl₂) → 46

46 → (Pd / C, H₂) → 47

47 → (Dess-Martin) → 48

Scheme 14

Scheme Section I

Schemes 1 to 3 are described in the examples.

Scheme 1

1

3

4

5

GS16573

Scheme 2

Cs_2CO_3, TfO—P(=O)(OBn)(OBn)

THF, r.t.

4

6
GS16574

Pd / C, H_2

EtOH

7
GS16575

Scheme 3

1

9

10
GS17089

11
GS17090

Scheme Section J

Schemes 1-4 are described in the examples.

Scheme 1

A

1

2

3   3a-e

Scheme 2

A

1

2

3

4

3 →

5

6

Scheme 3

A

1

2

3a : R = -Bn
3b : R = -Et

4a : R = -Bn
4b : R = -Et

5a : R = -Bn
5b : R = -Et

6
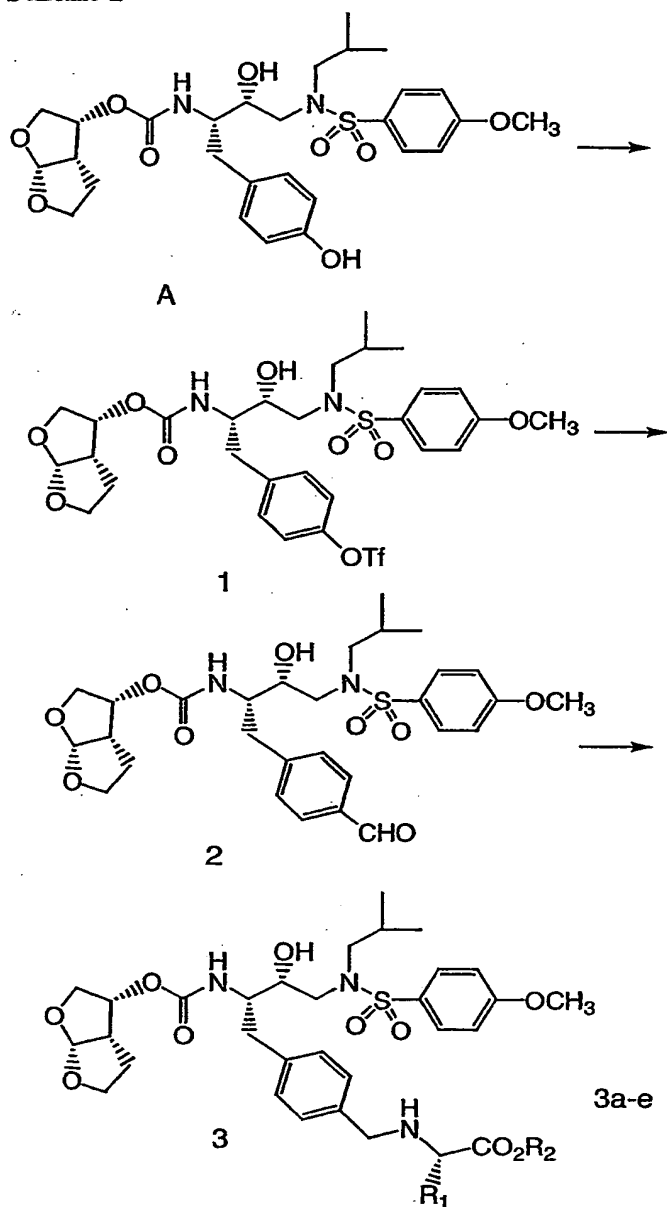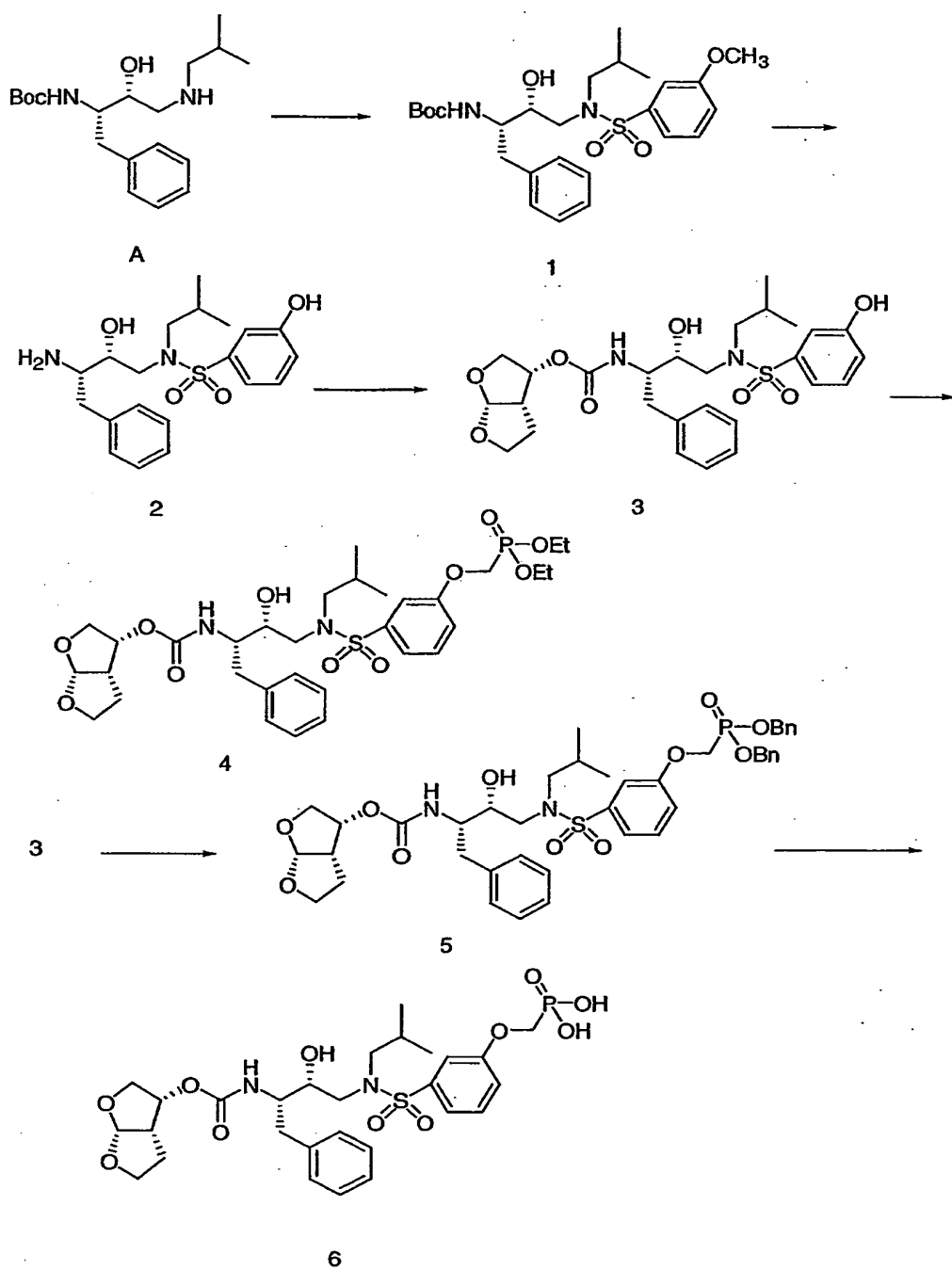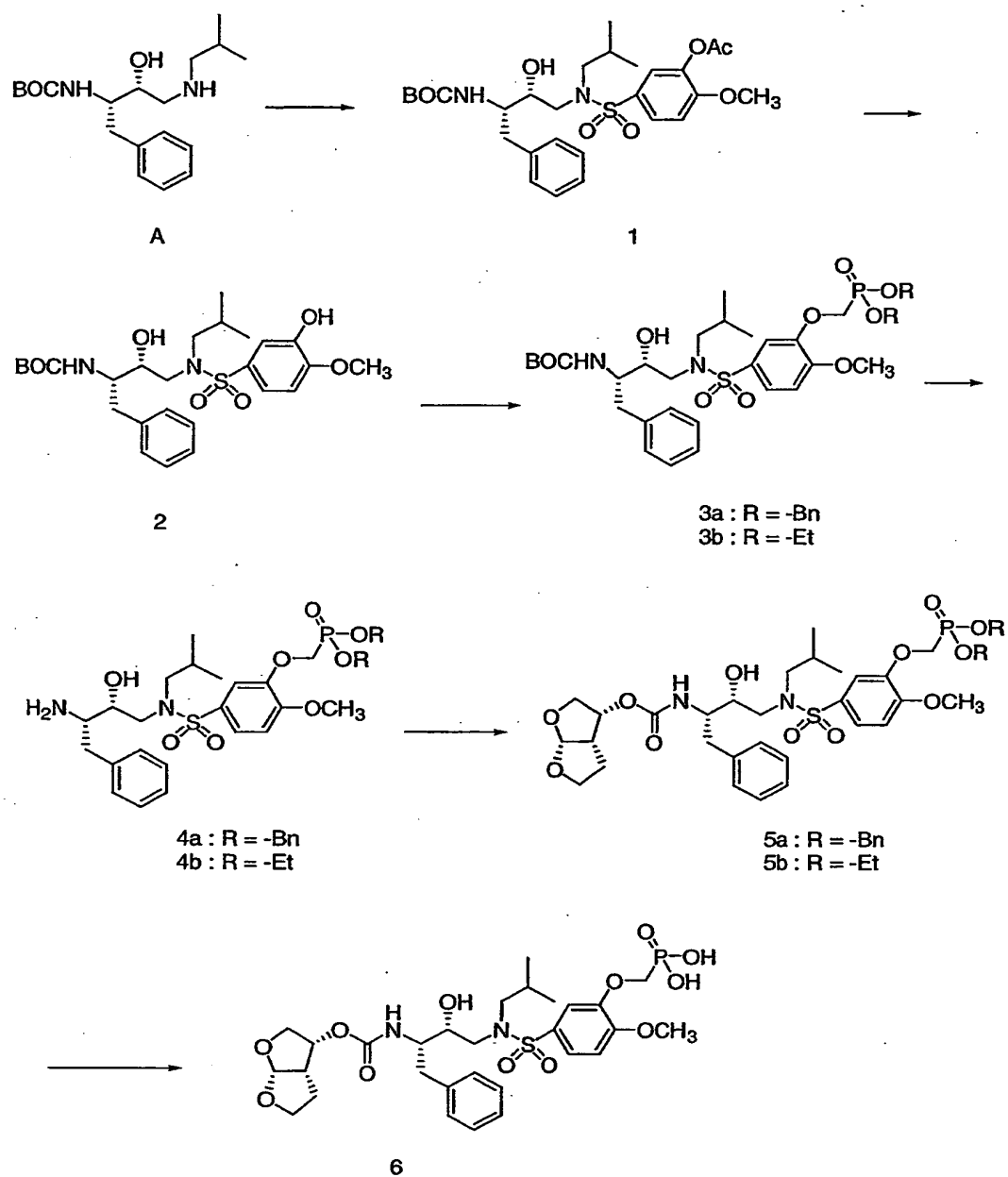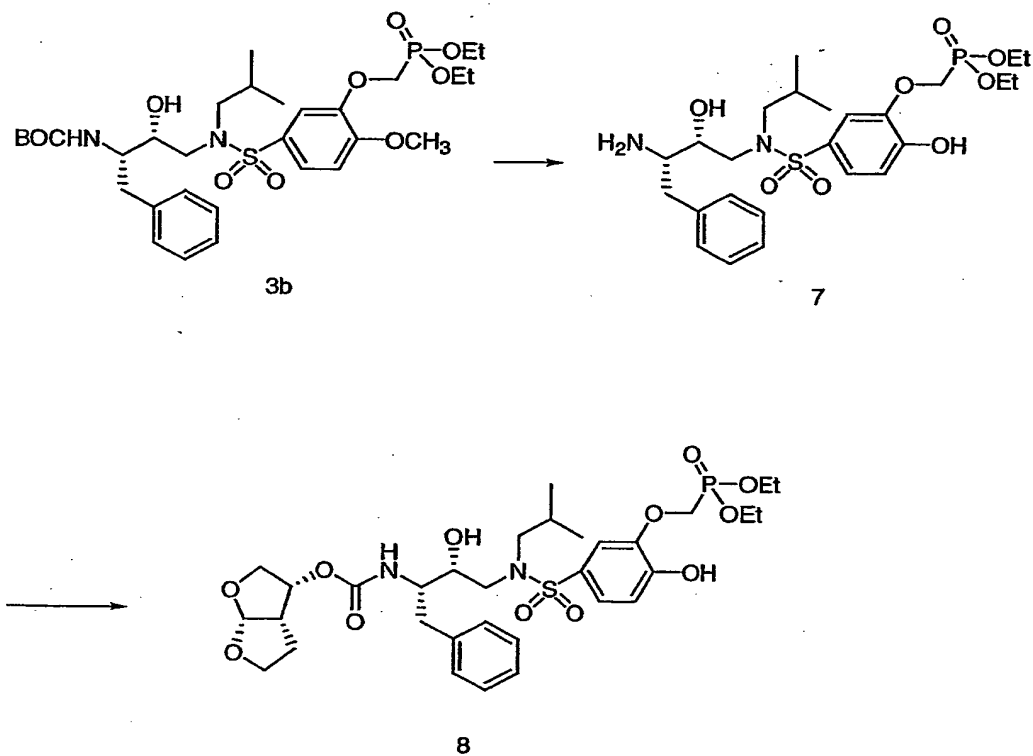
Scheme 4

Scheme Section K
Schemes 1-9 are described in the examples.

5   **Scheme 1**

1

2

DCC, Pyridine

2 hrs., 70°C

3

Scheme 2
10

1

+ HCl • H₂N

4

DCC, Pyridine

1 hr., 60°C

5

Scheme 3

8

Scheme 4

5

Scheme 5

6   Phenol, DCC
                     ————————————→
                     70°C, pyridine

10

5

Scheme 6

10   NaOH (1N)
                     ————————————→
                     0°C, acetonitrile
                     Dowex H+

1

Scheme 7

11   +

12

$\xrightarrow{\begin{array}{c} Cs_2CO_3 \\ \hline THF,\ r.t. \end{array}}$

9

5   **Scheme 8**

13

$\xrightarrow{\begin{array}{c} BBr_3 \\ \hline DCM,\ 0°C\ to\ r.t. \end{array}}$

14

Scheme 9

14

+

15

DMAP
————→
CH₃CN, r.t.

16

5

Scheme Section L

Schemes 1-9 are described in the examples.

Scheme 1

Synthesis of P1-Phosphonic ester

1

2

3

4

5

Scheme 2

11

5
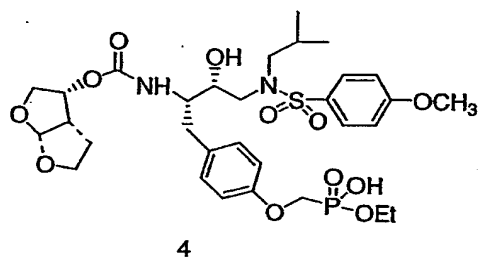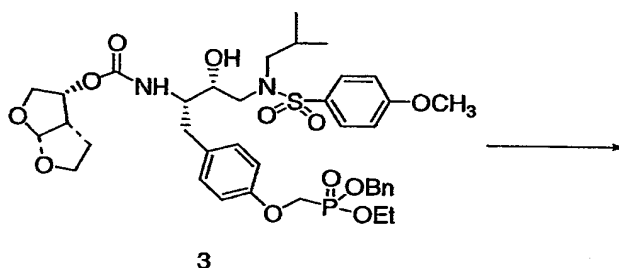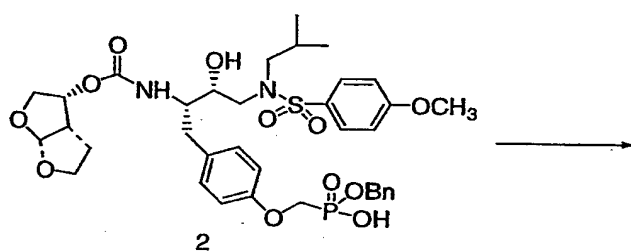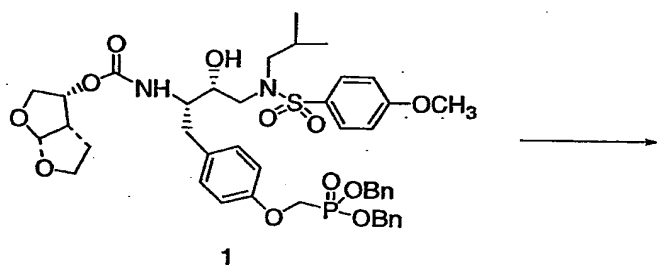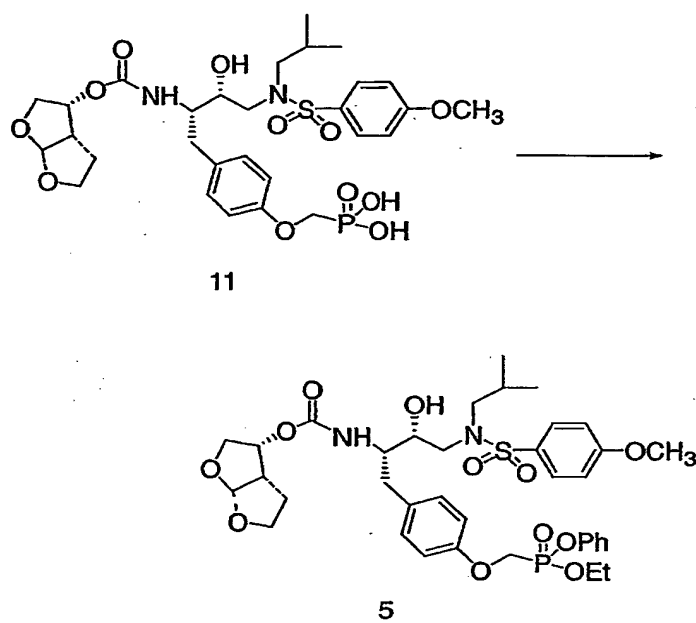
Scheme 3

Synthesis of P2'-Amino-P1-Phosphonic ester
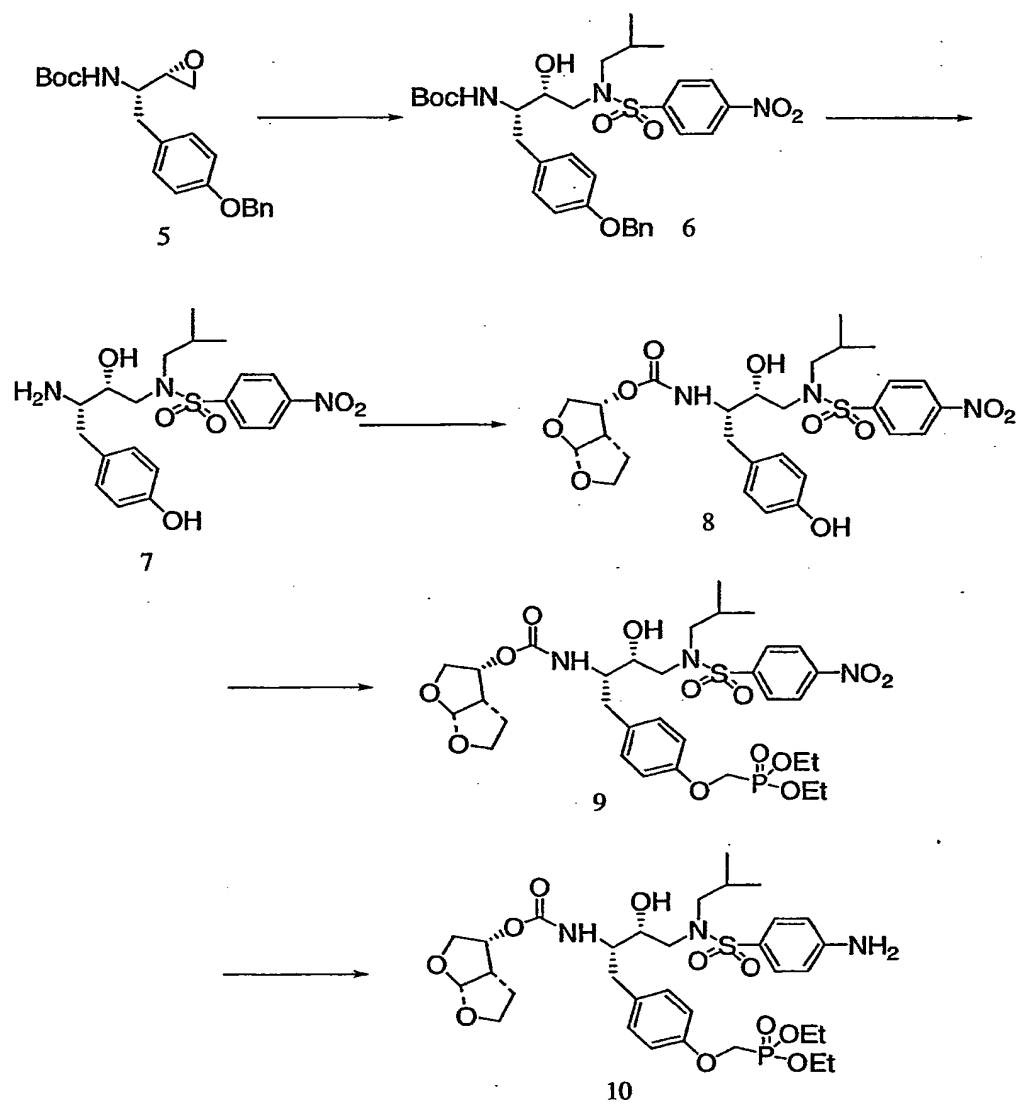
Scheme 4

Synthesis of Bisamidates

11
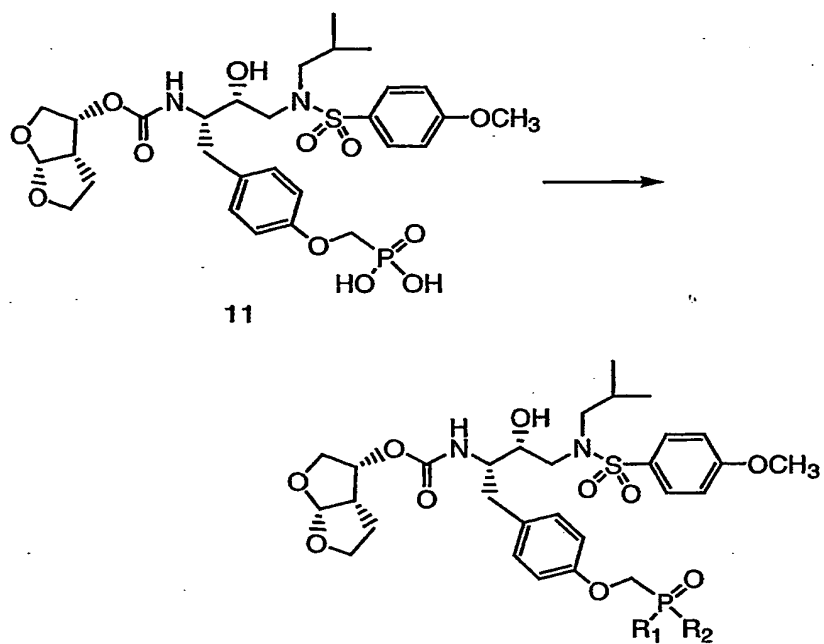
16 a,b,j and k

5

Compound	R₁	R₂
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Scheme 5

Synthesis of Monoamidates

29

30
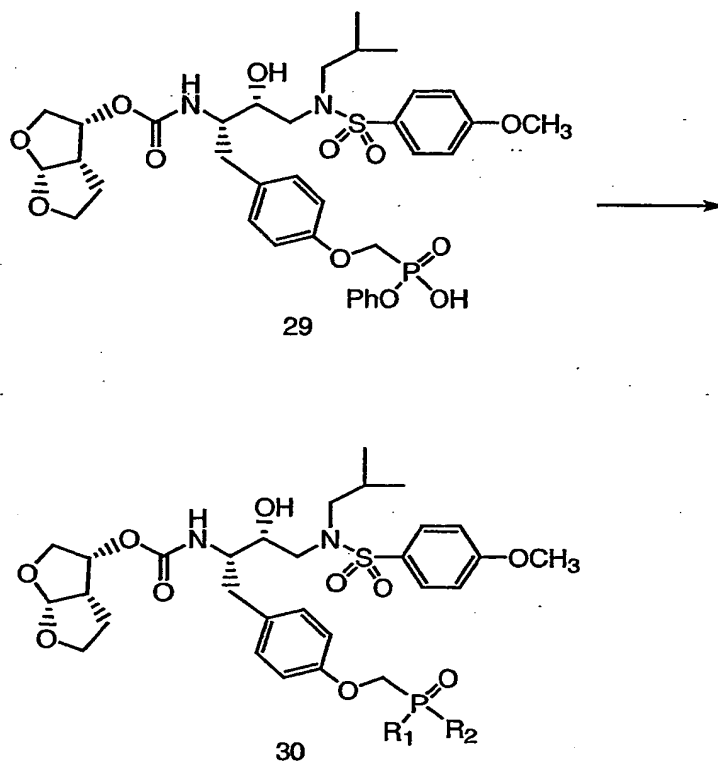
5

Compound	R₁	R₂
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Scheme 6

2

30e
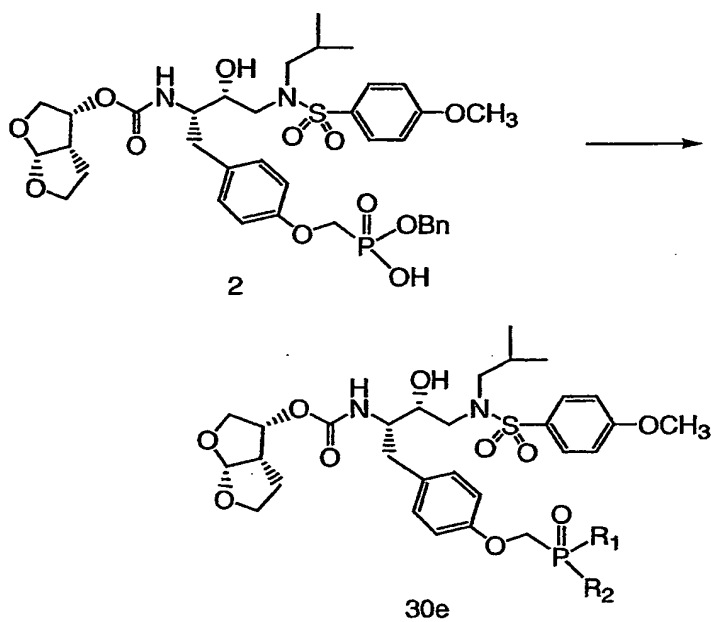
Scheme 7

Synthesis of Lactates
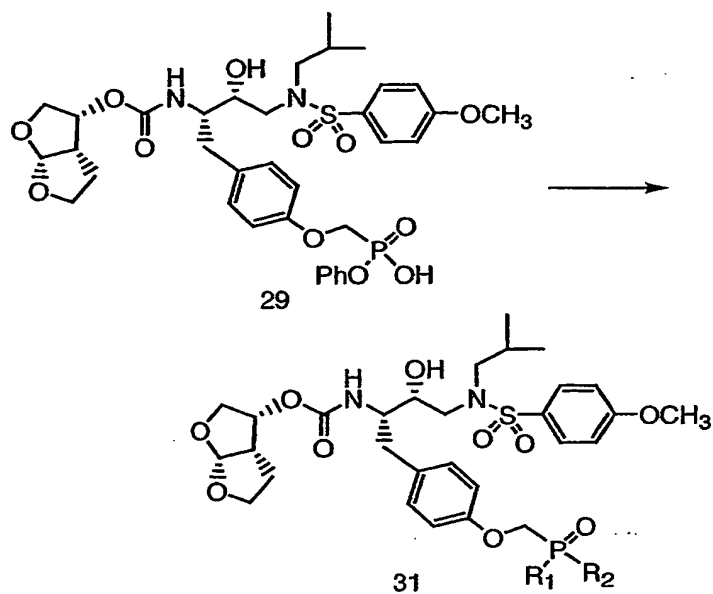
Compound	R₁	R₂
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Scheme 8
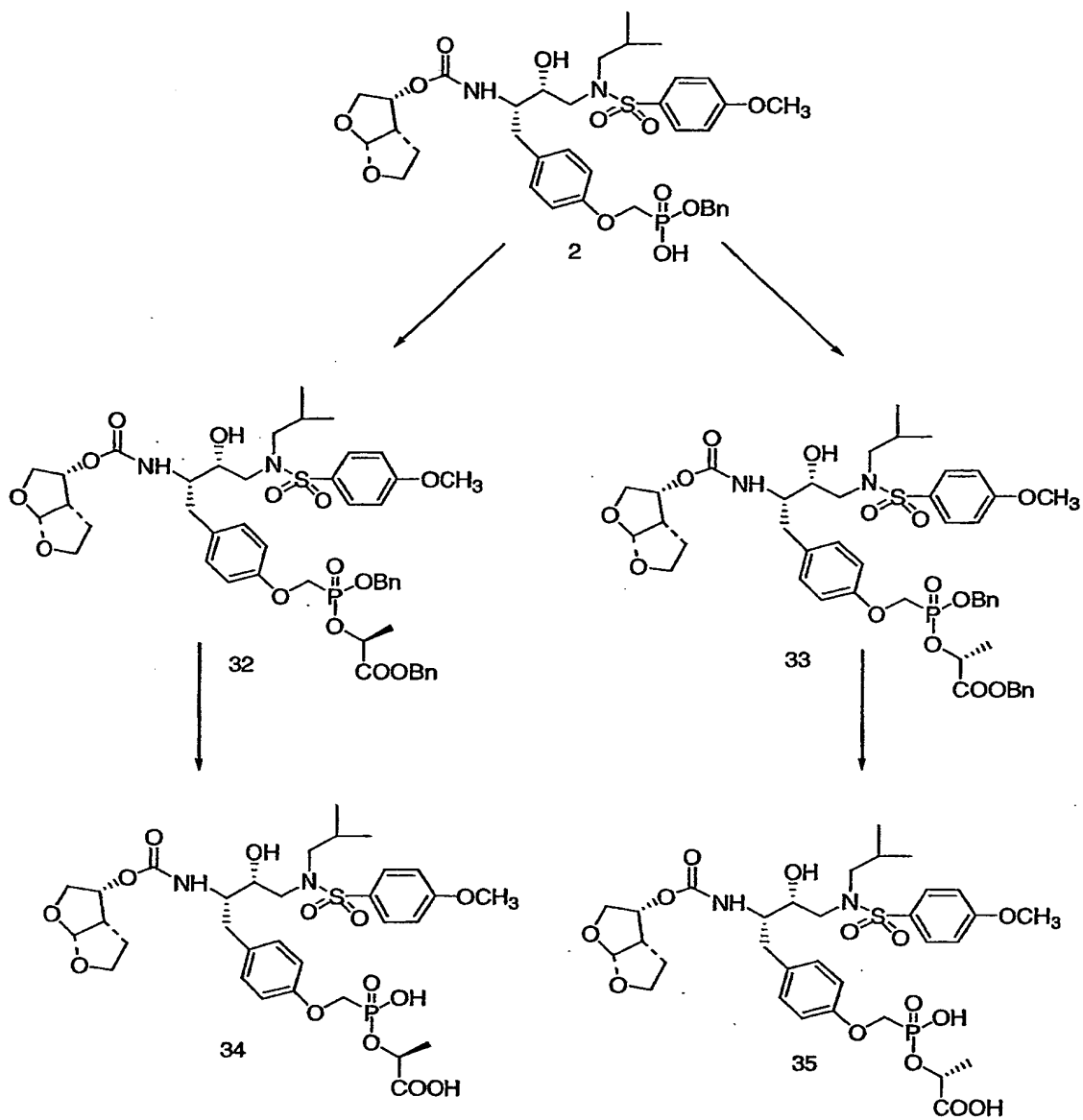
Scheme 9

Synthesis of Bislactate

11

36

5
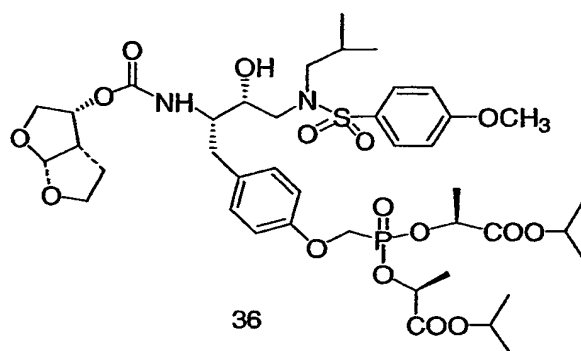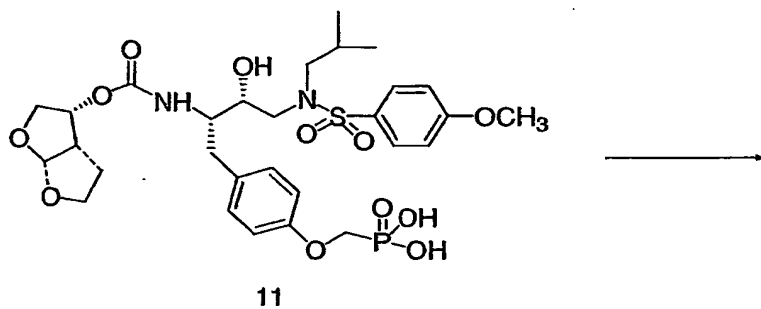
Examples

The following Examples refer to the Schemes.

5   Some Examples have been performed multiple times. In repeated Examples, reaction
conditions such as time, temperature, concentration and the like, and yields were within
normal experimental ranges. In repeated Examples where significant modifications were
made, these have been noted where the results varied significantly from those described. In
Examples where different starting materials were used, these are noted. When the repeated
10   Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl
ester", this intends that an otherwise present group, in this case typically a methyl ester, is
taken to be the same group modified as indicated.

Example Section A

15   **Example 1**

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (11 g, 30
mmol, Fluka) in dry THF (55 mL) at -25-30°C (external bath temperature) was added
isobutylchloroformate (3.9 mL, 30 mmol) followed by the slow addition of
N.methylmorpholine (3.3 mL, 30 mmol). The mixture was stirred for 25 min, filtered while
20   cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to
- 25°C and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica
Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The
reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to
warm to room temperature while stirring overnight for 15 h. The solvent was evaporated
25   under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated
NaHCO$_3$, saturated NaCl, dried (MgSO$_4$), filtered and evaporated to a pale yellow solid. The
crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (10.9 g, 92%)
which was used directly in the next step.

30   **Example 2**

Chloroketone 2: To a suspension of diazoketone 1 (10.8 g, 27 mmol) in ether (600 mL) at
0°C was added 4M HCl in dioxane (7.5 mL, 30 mmol). The solution was removed from the
cooling bath, and allowed to warm to room temperature at which time the reaction was stirred
1 h. The reaction solvent was evaporated under reduced pressure to give a solid residue that

was dissolved in ether and passed through a short column of silica gel. The solvent was evaporated to afford the chloroketone (10.7 g, 97%) as a solid.

Example 3

5   Chloroalcohol 3: To a solution of chloroketone 2 (10.6 g, 26 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 3-4°C (internal temperature). A solution of NaBH$_4$ (1.5 g, 39 mmol) in water (5 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1h at 0°C and saturated KHSO$_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried

10   (MgSO$_4$) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH$_3$CN:H$_2$O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 µL; column: 5µ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (4.86g,

15   >99% diastereomeric purity by HPLC analysis) as a white solid.

Example 4

Epoxide 5: A solution of chloroalcohol 3 (4.32 g, 10.6 mmol) in EtOH (250 mL) and THF (100 mL) was treated with K$_2$CO$_3$ (4.4g, 325 mesh, 31.9 mmol) and the mixture was stirred

20   for at room temperature for 20h. The reaction mixture was filtered and was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NaCl, dried (MgSO$_4$), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford the epoxide (3.68 g, 94%) as a white solid.

25

Example 5

Sulfonamide 6: To a suspension of epoxide 5 (2.08 g, 5.6 mmol) in 2-propanol (20 mL) was added isobutylamine (10.7 mL, 108 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$

30   (20 mL) and cooled to 0°C. N,N'-diisopropylethylamine (1.96 mL, 11.3 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.45 g, 7 mmol) in CH$_2$Cl$_2$ (5 mL) and the solution was stirred for 40 min at 0°C, warmed to room temperature and

evaporated under reduced pressure. The residue was partitioned between EtOAc and
saturated NaHCO₃. The organic phase was washed with saturated NaCl, dried (MgSO₄),
filtered and evaporated under reduced pressure. The crude product was recrystallized from
EtOAc/hexane to give the sulfonamide (2.79 g, 81%) as a small white needles: mp 122-
5   124°C (uncorrected).

Example 6

Carbamate 7: A solution of sulfonamide 6 (500 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) at 0°C
was treated with trifluoroacetic acid (5 mL). The solution was stirred at 0°C for 30 min and
10   was removed from the cold bath stirring for an additional 30 min. Volatiles were evaporated
under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated
NaHCO₃. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic
extracts were washed with saturated NaCl, dried (MgSO₄), filtered, and evaporated under
reduced pressure. The residue was dissolved in CH_3CN (5 mL) and was treated with (3R,
15   3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (263 mg, 0.89 mmol,
prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-
dimethylaminopyridine (197 mg, 1.62 mmol). After stirring for 1.5h at room temperature,
the reaction solvent was evaporated under reduced pressure and the residue was partitioned
between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K_2CO_3,
20   and then was washed with saturated NaCl, dried (MgSO₄), filtered, and evaporated under
reduced pressure. The crude product was purified by chromatography on silica gel (1/1 -
EtOAc/hexane) affording the carbamate (454 mg, 83%) as a solid: mp 128-129°C (MeOH,
uncorrected).

25   Example 7

Phenol 8: A solution of carbamate 7 (1.15 g, 1.7 mmol) in EtOH (50 mL) and EtOAc (20
mL) was treated with 10% Pd/C (115 mg) and was stirred under H₂ atmosphere (balloon) for
18h. The reaction solution was purged with N₂, filtered through a 0.45 μM filter and was
evaporated under reduced pressure to afford the phenol as a solid that contained residual
30   solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example 8

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (527 mg, 1.8 mmol) in CH₂Cl₂ (5 mL) was treated with 2,6-lutidine (300 µL, 2.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (360 µL, 2.1 mmol) was added and the reaction mixture was stirred for 15 min and

5　then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M H₃PO₄, saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure to afford triflate 9 (697 mg, 91%) as an oil which was used directly without any further purification. To a solution of phenol 8 (775 mg, 1.3 mmol) in THF (5 mL) was added

10　Cs₂CO₃ (423 mg, 1.3 mmol) and triflate 9 (710 mg, 1.7 mmol) in THF (2 mL). After stirring the reaction mixture for 30 min at room temperature additional Cs₂CO₃ (423 mg, 1.3 mmol) and triflate (178 mg, 0.33 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried (MgSO₄), filtered and

15　evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/CH₂Cl₂) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C, the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (836 mg, 76%) as a white solid:

20　.^{1}H NMR (CDCl₃) δ 7.66 (d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR (CDCl₃) δ 18.7; MS (ESI) 853 (M+H).

Example 9

25　Phosphonic acid 11: A solution of dibenzylphosphonate 10 (0.81 g) was dissolved in EtOH/. EtOAc (30mL/10 mL), treated with 10% Pd/C (80 mg) and was stirred under H₂ atmosphere (balloon) for 1.5h. The reaction was purged with N₂, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45 µM filter. After evaporation of the filtrate,

30　the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (634 mg, 99%) as a white solid: ^{1}H NMR (CDCl₃) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89

(s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m,

1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR (CDCl$_3$)

δ 16.2; MS (ESI) 671 (M-H).

5   Example 10

Diethylphosphonate 13: Triflate 12 was prepared from diethyl hydroxymethylphosphonate

(2g, 11.9 mmol), 2,6-lutidine (2.1 mL, 17.9 mmol), and trifluoromethanesulfonic anhydride

(2.5 mL, 14.9 mmol) as described for compound 9. To a solution of phenol 8 (60 mg, 0.10

mmol) in THF (2 mL) was added Cs$_2$CO$_3$ (65mg, 0.20 mmol) and triflate 12 (45 mg, 0.15

10   mmol) in THF (0.25 mL). The mixture was stirred at room temperature for 2h and additional

triflate (0.15 mmol) in THF (0.25 mL) was added. After 2h the reaction mixture was

partitioned between EtOAc and saturated NaCl. The organic phase was dried (MgSO$_4$),

filtered, and evaporated under reduced pressure. The crude product was chromatographed on

silica gel (EtOAc) to give a residue that was purified by chromatography on silica gel (5% 2-

15   propanol /CH$_2$Cl$_2$) to afford the diethylphosphonate as a foam: ^{1}H NMR (CDCl$_3$) δ 7.66 (d,

2H), 7.10 (d, 2H), 6.94 (d, 2H), 6.82 (d, 2H), 5.60 (d, 1H), 4.97 (d, 2H), 4.23-4.13 (m, 6H),

3.93-3.62 (m, 10H), 3.12-2.68 (m, 7H), 1.84-1.44 (m, 3H), 1.31 (t, 6H), 0.88-0.82 (2d, 6H);

^{31}P NMR (CDCl$_3$) δ 17.7; MS (ESI) 729 (M+H).

20   Example 11

Diphenylphosphonate 14: To a solution of 11 (100mg, 0.15 mmol) and phenol (141 mg, 1.5

mmol) in pyridine (1.5 mL) was added N, N-diisopropylcarbodiimide (50 μL, 0.38 mmol). The

solution was stirred for 31h at room temperature and for 20h at 50°C. The solvent was evaporated

under reduced pressure and the residue was purified by chromatography on silica gel eluting

25   (EtOAc) to provide diphenylphosphonate 14 (16 mg) as a foam: ^{31}P NMR (CDCl$_3$) δ 10.9; MS

(ESI) 847 (M+Na).

Example 12

Bis-Poc-phosphonate 15: To a solution of 11 (50 mg, 0.74 mmol) and isopropylchloromethyl

30   carbonate (29 mg, 0.19 mmol) in DMF (0.5 mL) was added triethylamine (26 μL, 0.19

mmol) and the solution was heated at 70°C (bath temperature) for 4.5h. The reaction was

concentrated under reduced pressure and the residue was purified by preparative layer

chromatography (2% 2-propanol/ CH$_2$Cl$_2$) to afford 15 (7 mg): ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.15 (d, 2H); 7.01 (d, 2H), 6.93 (d, 2H), 5.80-5.71 (m, 4H), 5.67 (d, 1H), 5.07-4.87 (m, 4H), 4.35 (d, 2H), 4.04-3.68 (m, 10H), 3.13 (dd, 1H), 3.04-2.90 (m, 5H), 2.79 (dd, 1H), 1.88-1.50 (m, 3H+H$_2$O peak), 1.30 (m, 12H), 0.93 (d, 3H), 0.88 (d, 3H); ^{31}P NMR (CDCl$_3$) δ 19.6.

Example 13

Synthesis of Bisamidates 16a-j. Representative Procedure, Bisamidate 16f: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) and (S)-2-aminobutyric acid butyl ester hydrochloride (116 mg, 0.59 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16f (106 mg, 75%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, 2H), 7.15 (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 5.67 (d, 1H), 5.05 (m, 1H), 4.96 (d, 1H), 4.19-3.71 (m overlapping s, 18H,), 3.42 (t, 1H), 3.30 (t, 1H), 3.20 (dd, 1H), 3.20-2.97 (m, 4H), 2.80 (dd, 2H), 1.87-1.54 (m, 19H), 1.42-1.35 (4H), 0.97-0.88 (m, 18H); ^{31}P NMR (CDCl$_3$) δ 20.3; MS (ESI) 955 (M+H).

Compound	R$_1$	R$_2$	Amino Acid
16a	H	Et	Gly
16b	H	Bu	Gly
16c	Me	Et	Ala
16d	Me	Bu	Ala
16e	Et	Et	Aba[1]
16f	Et	Bu	Aba[1]
16g	iBu	Et	Leu
16h	iBu	Bu	Leu
16i	Bn	Et	Phe
16j	Bn	Bu	Phe

[1] Aba, 2-aminobutyric acid

Example 14

Diazo ketone 17: To a solution of N-tert-Butoxycarbonyl-p-bromo-L-phenylalanine (9.9 g, 28.8 mmol, Synthetech) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.74 mL, 28.8 mmol) followed by the slow addition of N-

methylmorpholine (3.16 mL, 28.8 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to - 25°C and diazomethane (~50 mmol, generated from 15 g diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The

5 reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was suspended in ether, washed with water, saturated NaHCO₃, saturated NaCl, dried (MgSO₄), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford diazo ketone 17 (9.73 g, 90%)

10 which was used directly in the next step.

Example 15

Chloroketone 18: To a solution of diazoketone 17 (9.73 g, 26 mmol) in ether (500 mL) at 0°C was added 4M HCl in dioxane (6.6 mL, 26 mmol). The solution was stirred for 1 h at

15 0°C and 4M HCl in dioxane (1 mL) was added. After 1h, the reaction solvent was evaporated under reduced pressure to afford the chloroketone 18 (9.79 g, 98%) as a white solid.

Example 16

20 Chloroalcohol 19: A solution of chloroketone 18 (9.79g, 26 mmol) in THF (180 mL) and water (16 mL) was cooled to 0°C (internal temperature). Solid NaBH₄ (2.5 g, 66 mmol) was added in several portions over a period of 15 min while maintaining the internal temperature below 5°C. . The mixture was stirred for 45 min and saturated KHSO₄ was slowly added until the pH<3. The mixture was partitioned between EtOAc and water. The aqueous phase was

25 extracted with EtOAc and the combined organic extracts were washed with brine, dried (MgSO₄) filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc, and was passed through a short column of silica gel, and the solvent was evaporated. The solid residue was recrystallized from EtOAc/hexane to afford the chloroalcohol 19 (3.84g) as a white solid.

30

Example 17

Epoxide 21: A partial suspension of chloroalcohol 19 (1.16g, 3.1 mmol) in EtOH (50 mL) was treated with K₂CO₃ (2g, 14.5 mmol) and the mixture was stirred for 4 h at room

temperature. The reaction mixture was diluted with EtOAc, filtered, and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl, and the organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford epoxide 21 (1.05g, 92%) as a white crystalline solid.

5

Example 18

Sulfonamide 22: To a solution of epoxide 21 (1.05g, 3.1 mmol) in 2-propanol (40 mL) was added isobutylamine (6 mL, 61 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2

10   (20 mL) and cooled to 0°C. Triethylamine (642 µL, 4.6 mmol) was added followed by the addition of (634 mg, 3.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 2h at 0°C at which time the reaction solution was treated with additional triethylamine (1.5 mmol) and 4-methoxybenzenesulfonyl chloride (0.31 mmol). After 1.5 h, the reaction solution was evaporated under reduced pressure. The residue was partitioned between EtOAc and cold

15   1M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The crude product was purified on silica gel (15/1 - CH_2Cl_2/EtOAc) to afford 1.67g of a solid which was recrystallized from EtOAc/hexane to give sulfonamide 22 (1.54g, 86%) as a white crystalline solid.

20

Example 19

Silyl ether 23: To a solution of the sulfonamide 22 (1.53g, 2.6 mmol) in CH_2Cl_2 (12 mL) at 0°C was added N,N-diisopropylethylamine (0.68 mL, 3.9 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (0.75 mL, 3.3 mmol). The reaction solution

25   was stirred for 1 h at 0°C and was warmed to room temperature, stirring for 17 h. Additional N,N-diisopropylethylamine (3.9 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.6 mmol) was added, stirred for 2.5h, then heated to reflux for 3h and stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc and cold 1M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, and was

30   dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified on silica gel (2/1 - hexane/ether) to afford silyl ether 23 (780 mg, 43%) as an oil.

Example 20

Phosphonate 24: A solution of 23 (260 mg, 0.37 mmol), triethylamine (0.52 mL, 3.7 mmol), and diethylphosphite (0.24 mmol, 1.85 mmol) in toluene (2 mL) was purged with argon and to the solution was added (Ph₃P)₄Pd (43 mg, 10 mol%). The reaction mixture was heated at 110°C (bath temperature) for 6 h, and was then allowed to stir at room temperature for 12h.

5 The solvent was evaporated under reduced pressure and the residue was partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic extracts were washed with saturated NaCl, dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2/1 - ethyl acetate/hexane) to afford diethylphosphonate 24 (153 mg, 55%).

10

Example 21

Phosphonic acid 26: To a solution of 24 (143 mg) in MeOH (5 mL) was added 4N HCl (2 mL). The solution was stirred at room temperature for 9h and was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected by filtration to

15 provide hydrochloride salt 25 (100 mg, 92%) as a white powder. To a solution of X (47 mg, 0.87 mmol) in CH₃CN (1 mL) at 0°C was added TMSBr (130 µL, 0.97 mmol). The reaction was warmed to room temperature and stirred for 6.5h at which time TMSBr (0.87 mmol) was added and stirring was continued for 16h. The solution was cooled to 0°C and was quenched with several drops of ice-cold water. The solvents were evaporated under reduced pressure

20 and the residue was dissolved in several milliters of MeOH and treated with propylene oxide (2 mL). The mixture was heated to gentle boiling and evaporated. The residue was triturated with acetone and the solid was collected by filtration to give phosphonic acid 26 (32 mg, 76%) as a white solid.

25 Example 22

Phosphonate 27: To a suspension of 26 (32 mg, 0.66 mmol) in CH₃CN (1 mL) was added bis(trimethylsilyl)acetamide (100 µL, 0.40 mmol) and the solution was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH₃CN (1 mL). To this solution was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-

30 b]furan-2-yl 4-nitrophenyl carbonate (20 mg, 0.069 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), N,N-diisopropylethylamine (35 µL, 0.20 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred for 22h at room temperature, diluted with water (0.5 mL) and was stirred with IR 120 ion exchange resin (325

-1262-

mg, H⁺ form) until the pH was <2. The resin was removed by filtration, washed with methanol and the filtrate was concentrated under reduced pressure. The residue was dissolved water, treated with solid NaHCO₃ until pH=8 and was evaporated to dryness. The residue was dissolved in water and was purified on C18 reverse phase chromatography

5   eluting with water followed by 5%, 10% and 20% MeOH in water to give the disodium salt 27 (24 mg) as a pale yellow solid: ¹H NMR (D₂O) δ 7.72 (d, 2H), 7.52 (dd, 2H), 7.13 (dd, 2H), 7.05 (d, 2H), 5.58 (d, 1H), 4.87 (m, 1H), 3.86-3.53 (m overlapping s, 10H), 3.22 (dd, 1H), 3.12-2.85 (6H), 2.44 (m, 1H), 1.83 (m, 1H), 1.61 (m, 1H)1.12 (dd, 1H), 0.77 (m, 6H); ³¹P NMR (D₂O) δ 11.23 ; MS (ESI) 641 (M-H).

10

Example 23

Diethylphosphonate 28: To a solution of 25 (16 mg, 0.028 mmol) in CH₃CN (0.5 mL) was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (9 mg, 0.031 mmol), N,N-diisopropylethylamine (20 µL, 0.11 mmol), and N,N-dimethylaminopyridine

15   (catalytic amount). The solution was stirred at room temperature for 48 h and was then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO₃. The organic phase was washed with saturated NaHCO₃, saturated NaCl, and was dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.5-5% 2-propanol/CH₂Cl₂). The residue obtained

20   was further purified by preparative layer chromatography (5% MeOH/CH₂Cl₂) followed by column chromatography on silica gel (10% 2-propanol/CH₂Cl₂) to afford diethylphosphonate 28 (7 mg) as a foam: ¹H NMR (CDCl₃) δ 7.72-7.66 (m, 4H), 7.32-7.28 (2H), 6.96 (d, 2H), 5.60 (d, 1H), 4.97 (m, 2H), 4.18-4.01 (m, 4H), 3.94-3.60 (m overlapping s, 10H), 3.15-2.72 (m, 7H), 1.78 (m, 1H), 1.61 (m+H₂O, ~3H), 1.28 (t; 6H), 0.86 (m, 6H); ³¹P NMR (CDCl₃) δ

25   18.6 ; MS (ESI) 699 (M+H).

Prospective Example 24

Diphenyl phosphonate 14 is treated with aqueous sodium hydroxide to provide monophenyl phosphonate 29 according to the method found in J. Med. Chem. 1994, 37, 1857.

30   Monophenyl phosphonate 29 is then converted to the monoamidate 30 by reaction with an amino acid ester in the presence of Ph₃ and 2,2'-dipyridyl disulfide as described in the synthesis of bisamidate 16f. Alteratively, monoamidate 30 is prepared by treating 29 with an

amino acid ester and DCC. Coupling conditions of this type are found in Bull. Chem. Soc. Jpn. 1988, 61, 4491.

Example 25

5   Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (25 g, 67 mmol, Fluka) in dry THF (150 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (8.9 mL, 69 mmol) followed by the slow addition of N.methylmorpholine (37.5 mL, 69 mmol). The mixture was stirred for 40 min, and diazomethane (170 mmol, generated from 25 g 1-methyl-3-nitro-1-nitroso-guanidine

10 according to Aldrichimica Acta 1983, 16, 3) in ether (400 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min allowing the bath to warm to room temperature while stirring overnight for 4 h. The mixture was bubbled with N2 for 30 min., washed with water, saturated NaHCO3, saturated NaCl, dried (MgSO4), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried

15 to afford the diazo ketone (26.8 g, 99%) which was used directly in the next step.

Example 26

Chloroketone 2: To a suspension of diazoketone 1 (26.8 g, 67 mmol) in ether/THF (750 mL, 3/2) at 0°C was added 4M HCl in dioxane (16.9 mL, 67 mmol). The solution was stirred at

20 0°C for 2 hr. The reaction solvent was evaporated under reduced pressure to give the chloroketone (27.7 g, 97%) as a solid.

Example 27

Chloroalcohol 3: To a solution of chloroketone 2 (127.1 g, 67 mmol) in THF (350 mL) was

25 added water (40 mL) and the solution was cooled to 3-4°C (internal temperature). NaBH4 (6.3 g, 168 mmol) was added in portions. The mixture was stirred for 1h at 0°C and the solvents were removed. The mixture was diluted with ethyl acetate and saturated KHSO4 was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried (MgSO4) filtered and evaporated under reduced pressure. The

30 crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH3CN:H2O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 μL; column: 5μ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor

diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (12.2g, >96% diastereomeric purity by HPLC analysis) as a white solid.

Example 28

5   Epoxide 5: To a solution of chloroalcohol 3 (12.17 g, 130 mmol) in EtOH (300 mL) was added KOH/EtOH solution (0.71N, 51 mL, 36 mmol). The mixture was stirred for at room temperature for 1.5h. The reaction mixture was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NH4Cl, dried (MgSO4), filtered, and evaporated under reduced pressure to afford

10   the epoxide (10.8 g, 97%) as a white solid.

Example 29

Sulfonamide 6: To a suspension of epoxide 5 (10.8 g, 30 mmol) in 2-propanol (100 mL) was added isobutylamine (129.8 mL, 300 mmol) and the solution was refluxed for 1 hr. The

15   solution was evaporated under reduced pressure to give a crude solid. The solid (42 mmol) was dissolved in CH2Cl2 (200 mL) and cooled to 0°C. Triethylamine (11.7 mL, 84 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (8.68 g, 42 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO3.

20   The organic phase was washed with saturated NaCl, dried (MgSO4), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (23.4 g, 91%) as a small white needles: mp 122-124°C (uncorrected).

Example 30

25   Carbamate 7: A solution of sulfonamide 6 (6.29 mg, 10.1 mmol) in CH2Cl2 (20 mL) was treated with trifluoroacetic acid (10 mL). The solution was stirred for 3 hr. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase were washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried (MgSO4), filtered, and evaporated under reduced pressure. The residue was

30   dissolved in CH3CN (60 mL), cooled to 0°C and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (298.5 g, 10 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (2.4 g, 20 mmol). After stirring for 1h at 0°C, the reaction solvent was evaporated under

reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K$_2$CO$_3$, and then was washed with saturated NaCl, dried (MgSO$_4$), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (5.4

5 g, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

Example 31

Phenol 8: A solution of carbamate 7 (5.4 g, 8.0 mmol) in EtOH (260 mL) and EtOAc (130 mL) was treated with 10% Pd/C (540 mg) and was stirred under H$_2$ atmosphere (balloon) for

10 3h. The reaction solution stirred with celite for 10 min, and passed through a pad of celite. The filtrate was evaporated under reduced pressure to afford the phenol as a solid (4.9 g) that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example 32

15 Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (3.1 g, 10.6 mmol) in CH$_2$Cl$_2$ (30 mL) was treated with 2,6-lutidine (1.8 mL, 15.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (2.11 mL, 12.6 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned

20 between ether and ice-cold water. The organic phase was washed with cold 1M H$_3$PO$_4$, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure to afford triflate 9 (3.6 g, 80%) as an oil which was used directly without any further purification. To a solution of phenol 8 (3.61 g, 6.3 mmol) in THF (90 mL) was added Cs$_2$CO$_3$ (4.1 g, 12.6 mmol) and triflate 9 (4.1 g, 9.5 mmol) in THF (10 mL). After stirring the reaction mixture

25 for 30 min at room temperature additional Cs$_2$CO$_3$ (6.96 g, 3 mmol) and triflate (1.26 g, 3 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-

30 propanol/CH$_2$Cl$_2$) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (3.43 g, 64%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.66

(d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR (CDCl$_3$) δ 18.7; MS (ESI) 853 (M+H).

5   Example 33

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (3.43 g) was dissolved in EtOH/ EtOAc (150 mL/50 mL), treated with 10% Pd/C (350 mg) and was stirred under H$_2$ atmosphere (balloon) for 3 h. The reaction mixture was stirred with celite, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure

10   and the residue was dissolved in MeOH and filtered with a 0.45 µM filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (2.6 g, 94%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89 (s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H),

15   2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR (CDCl$_3$) δ 16.2; MS (ESI) 671 (M-H).

Example Section B

There is no Section B in this application.

Example Section C

Example 1

Diphenyl phosphonate 31: To a solution of phosphonic acid 30 (11 g, 16.4 mmol) and phenol
(11 g, 117 mmol) in pyridine (100 mL) was added 1, 3-dicyclohexylcarbodiimide (13.5 g,
65.5 mmol). The solution was stirred at room temperature for 5 min and then at 70°C for 2h.
The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL)
and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The
residue was dissolved in ethyl acetate (250 mL) and acidified to pH = 4 by addition of HCl
(0.5 N) at 0°C. The mixture was stirred at 0°C for 0.5 h, filtered and the organic phase was
separated and washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced
pressure. The residue was purified on silica gel to give diphenyl phosphonate 31 (9 g, 67%)
as a solid. ^{31}P NMR (CDCl$_3$) d 12.5.

Example 2

Monophenyl phosphonate 32: To a solution of diphenylphosphonate 31 (9.0 g, 10.9 mmol) in
acetonitrile (400 mL) was added NaOH (1N, 27 mL) at 0°C. The reaction mixture was stirred at
0°C for 1 h, and then treated with Dowex (50WX8-200, 12 g). The mixture was stirred for 0.5 h
at 0°C, and then filtered. The filtrate was concentrated under reduced pressure and co-
evaporated with toluene. The residue was dissolved in ethyl acetate and hexane was added to
precipitate out the monophenyl phosphonate 32 (8.1 g, 100%). ^{31}P NMR (CDCl$_3$) d 18.3.

Example 3

Monoamidate 33a (R$_1$ = Me, R$_2$ = n-Bu): To a flask charged with monophenyl phosphonate
32 (4.0 g, 5.35 mmol) , was added L-alanine n-butyl ester hydrochloride (4.0 g, 22 mmol), 1,
3-dicyclohexylcarbodiimide (6.6 g, 32 mmol), and finally pyridine (30 mL) under nitrogen.
The resultant mixture was stirred at 60 – 70°C for 1 h, then cooled to room temperature and
diluted with ethyl acetate. The mixture was filtered and the filtrate was concentrated under
reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2 N) and the
organic layer was separated. The ethyl acetate phase was washed with water, saturated
NaHCO$_3$, dried over MgSO4 , filtered and concentrated under reduced pressure. The residue
was purified on silica gel (pre-treated with 10% MeOH / CH$_3$CO$_2$Et, eluting with 40%
CH$_2$Cl$_2$ / CH$_3$CO$_2$Et and CH$_3$CO$_2$Et) to give two isomers of 33a in a total yield of 51%.

Isomer A (1.1 g): 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl$_3$) d

5 20.5. Isomer B (1.3 g) 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2-4.35 (m, 3H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl$_3$) d 19.4.

10 Example 4

Monoamidate 33b (R$_1$ = Me, R$_2$ = i-Pr) was synthesized in the same manner as 33a in 77% yield. Isomer A : 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d,

15 J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl$_3$) d 20.4. Isomer B: 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl$_3$) d 19.5.

Example Section D

Example 1

Cyclic Anhydride 1 (6.57 g, 51.3 mmol) was treated according to the procedure of Brown et

5　al., J. Amer. Chem. Soc. 1955, 77, 1089 -1091 to afford amino alcohol 3 (2.00g, 33%). *for intermediate 2* : ^{1}H NMR (CD$_3$OD) δ 2.40 (S, 2H), 1.20 (s, 6H).

Example 2

Amino alcohol 3　(2.0 g, 17 mmol) was stirred in 30 mL 1:1 THF: water. Sodium

10　Bicarbonate (7.2 g, 86 mmol) was added, followed by Boc Anhydride (4.1 g, 19 mmol). The reaction was stirred for 1 hour, at which time TLC in 5% methanol/DCM with ninhydrin stain showed completion. The reaction was partitioned between water and ethyl acetate. The organic layer was dried and concentrated, and the resulting mixture was chromatographed on silica in 1:1 hexane: ethyl acetate to afford two fractions, "upper" and "lower" each having

15　the correct mass. By NMR the correct product 4 was "lower" (0.56 g, 14%) ^{1}H NMR (CDCl$_3$) δ 3.7 (t, 2H), 3.0 (d,2H), 1.45 (t, 2H) 1.4 (s, 9H), 0.85 (s, 6H),

MS (ESI): 240 (M + 23).

Example 3

20　Sodium Hydride (60% emulsion in oil) was added to a solution of the alcohol 4 (1.1g, 5.2 mmol) in dry DMF in a 3-neck flask under dry nitrogen. Shortly afterward triflate 35 (2.4 g, 5.7 mmol) was added with stirring for 1.5 hrs. Mass spectrometry showed the presence of the starting material (240, M+23), thus 100 mg more 60% sodium hydride emulsion as well as ~1 g more triflate were added with an additional hour of stirring. The

25　reaction was quenched by the addition of saturated NaHCO$_3$ then partitioned between ethyl acetate and water. The organic layer was dried with brine and MgSO$_4$ and eluted on silica with 1:1 hexane:ethyl acetate to afford 5 (0.445 g, 15%). NMR showed some contamination with alcohol 4 starting material. ^{1}H NMR (CDCl$_3$): δ 7.28 (s, 10H), 5.00 (m, 4H), 3.70 (t, 2H), 2.94, (d, 2H), 1.44 (t, 2H), 1.40 (s, 9H), 0.83 (s, 6H) MS (ESI): 514 (M+23).

30

Example 4

Phosphonate ester 5 (0.445 g, 0.906 mmol) was stirred with with 20% TFA in DCM. (5 mL) TLC showed completion in 1 hr time. The reaction was azeotroped with toluene then run on

a silica gel column with 10% methanol in DCM. Subsequently, the product was dissolved in
ethyl acetate and shaken with saturated sodium bicarbonate: water (1:1), dried with brine and
magnesium sulfate to afford the free amine 6 (30mg, 8.5%). ^{1}H NMR (CDCl$_3$): δ 7.30 (s,
10H), 5.00 (m, 4H), 3.67 (d, 2H), 3.47, (t, 2H), 2.4-2.6 (brs) 1.45 (t, 2H), 0.82 (s, 6H), MS

5   (ESI): 393 (M+1).

Example 5

Amine 6 (30 mg, 0.08 mmol) and epoxide 7 (21 mg, 0.08 mmol) were dissolved in 2 mL
IprOH and heated to reflux for 1 hr then monitored by TLC in 10% MeOH/DCM. Added

10   ~20 mg more epoxide 7 and continued reflux for 1 hr. Cool to room temperature, dilute with
ethyl acetate, shake with water and brine, dry with magnesium sulfate. Silica gel
chromatography using first 5% then 10% MeOH in EtOAc yielded amine 8 (18 mg, 36%).
^{1}H NMR (CDCl$_3$): δ 7.30 (s, 10H), 7.20-7-14 (m, 5H), 5.25-4.91 (m, 4H), 3.83, (m, 1H), 3.71
(d, 2H) 3.64 (m, 1H), 3.54 (t, 2H), 3.02-2.61 (m, 5H), 2.65-2.36 (dd, 2H) (t, 2H), 1.30 (s, 9H)

15   0.93 (s, 9H) 0.83 (t, 2H) MS (ESI) 655 (M+1).

Example 6

Amine 8 (18 mg, 0.027 mmol) was dissolved in 1 mL DCM then acid chloride 9 (6 mg, 0.2
mmol) followed by triethylamine (0.004 mL, 0.029 mmol). The reaction was monitored by

20   TLC. Upon completion the reaction was diluted with DCM shaken with 5% citric acid,
saturated sodium bicarbonate, brine, and dried with MgSO$_4$. Purification on silica (1:1
Hexane:EtOAc) afforded sulfonamide 10 (10.5 mg, 46%). ^{1}H NMR (CDCl$_3$): δ 7.69 (d, 2H),
7.30 (s, 10H), 7.24-7-18 (m, 5H), 5.00 (m, 4H), 4.73, (d, 1H), 4.19 (s, 1H) 3.81 (m, 1H), 3.80
(s, 3H), 3.71 (d,2H), 3.57 (t, 2H), 3.11-2.95 (m, 5H) 2.75 (m,1H)1.25 (s, 1H), 0.90 (s, 6H)

25   MS (ESI) 847 (M+Na$^+$).

Example 7

Sulfonamide 10 (10.5 mg, 0.013 mmol) was stirred at room temperature in 20%
TFA/DCM. Once Boc deprotection was complete by TLC (1:1 Hexane:EtOAc) and MS, the

30   reaction was azeotroped with toluene. The TFA salt of the amine was dissolved in
acetonitrile (0.5 mg) and to this were added carbonate 11 (4.3 mg, 0.014 mmol) followed by
DMAP (4.6 mg, 0.038 mg). Stir at room temp until TLC (1:1 Hexane:EtOAc) shows
completion. Solvent was evaporated and the residue was redissolved in EtOAc then shaken

with saturated NaHCO₃. The organic layer was washed with water and brine, then dried with MgSO₄ Purification on silica with Hexane: EtOAc afforded compound 12 (7.1 mg, 50%). ¹H NMR (CDCl₃): δ 7.75 (d, 2H) 7.24-7.35 (15H) 6.98 (d, 2H), 5.62 (d, 1H) 5.04 (m, 4H) 4.98 (m, 1H) 4.03 (m, 1H), 3.85 (s, 3H), 3.61-3.91 (9H), 3.23-3.04 (5H) 2.85 (m, 1H), 2.74 (m,1H) 1.61 (d, 2H), 1.55 (m, 1H) 1.36 (m, 1H) 0.96 (d, 6H) MS (ESI): 903 (M+23).

Example 8

Compound 12 (6.1 mg, 0.007 mmol) was dissolved in 1 mL 3:1 EtOH:EtoAc. Palladium catalyst (10% on C, 1mg) was added and the mixture was purged three times to vacuum with 1 atmosphere hydrogen gas using a balloon. The reaction was stirred for 2 hrs, when MS and TLC showed completion. The reaction was filtered through Celite with EtOH washing and all solvent to was evaporated to afford final compound 13 (5mg, 100%). ¹H NMR (CD₃OD): δ 7.79 (d, 2H) 7.16-7.24 (5H) 7.09 (d, 2H) 5.58 (d, 1H) 4.92 (m, 1H) 3.97 (m, 1H), 3.92 (dd,1H) 3.89 (s, 3H) 3.66-3.78 (8H) 3.40 (d,1H), 3.37 (dd, 1H), 3.15 (m, 1H) 3.12 (dd,1H) 2.96 (d, 1H), 2.87 (m, 1H), 2.74 (m,1H) 2.53 (m, 1H) 1.70 (m, 2H), 1.53 (m, 1H) 1.32 (m, 1H) 1.04 (d, 6H) MS (ESI): 723 (M+23).

Example 9

Amino Alcohol 14 (2.67g, 25.9 mmol) was dissolved in THF with stirring and Boc Anhydride (6.78g, 31.1 mmol) was added. Heat and gas evolution ensued. TEA (3.97 mL, 28.5 mmol) was added and the reaction was stirred overnight. In the morning, the reaction was quenched by the addition of saturated NaHCO₃. The organic layer was separated out and shaken with water, dried with brine and MgSO₄ to afford 15 which was used without further purification. (100% yield) (some contamination): ¹H NMR (CDCl₃): δ 3.76 (t ,1H) 3.20, (d,2H), 2.97 (d, 2H), 1.44 (s, 9H), 0.85 (s, 6H).

Example 10

A solution of the alcohol 15 (500 mg, 2.45 mmol) in dry THF was cooled under dry N₂ with stirring. To this was added n-butyl lithium (1.29 mL, 2.71 mmol) as a solution in hexane in a manner similar to that described in Tetrahedron. 1995, 51 #35, 9737-9746. Triflate 35 (1.15 g, 2.71 mmol) was added neat with a tared syringe. The reaction was stirred for four hours, then quenched with saturated NaHCO₃. The mixture was then partitioned between water and EtOAc. The organic layer was dried with brine and MgSO₄, then chromatographed on silica

in 1:1 Hexane:EtOAc to afford phosphonate 16 (445mg, 38%) ^{1}H NMR (CDCl$_3$): δ 7.37 (m,

10H), 5.09 (m, 4H), 3.73-3.75 (m, 2H), 3.24 (s,2H), 3.02 (d, 2H), 1.43 (s, 9H), 0.86 (s, 6H).

Example 11

5   Phosphonate 16 (249 mg, 0.522 mmol) was stirred in 20% TFA/DCM for 1 hr. The reaction

was then azeotroped with toluene. The residue was re-dissolved in EtOAc, then shaken with

water: saturated NaHCO$_3$ (1:1). The organic layer was dried with brine and MgSO$_4$ and

solvent was removed to afford amine 17 (143 mg, 73%) ^{1}H NMR (CDCl$_3$): δ 7.30 (s, 10H),

5.05-4.99 (m, 4H), 3.73 (d, 2H), 3.23 (s, 2H), 2.46 (brs, 2H), 0.80 (s, 6H) ^{31}P NMR (CDCl$_3$):

10   δ 23.77 (s).

Example 12

Amine 17 (143 mg, 0.379 mmol) and epoxide 7 (95 mg, 0.360 mmol) were dissolved in 3 mL

IprOH and heated to 85°C for 1 hr. The reaction was cooled to room temperature overnight

15   then heated to 85°C for 1 hr more in the morning. The reaction was then diluted with EtOAc,

shaken with water, dried with brine MgSO$_4$ and concentrated. The residue was eluted on

silica in a gradient from 5% to 10% MeOH in DCM to afford compound 18 (33 mg, 14%).

Example 13

20   Mix compound 18 (33 mg, 0.051 mmol) and chlorosulfonyl compound 9 (11 mg, 0.054

mmol) in 2 mL DCM then add TEA (0.0075 mL, 0.054 mmol), stir for 5 hrs. TLC in 1:1

EtOAc: hexane shows reaction not complete. Place in freezer overnight. In the morning,

take out of freezer, stir for 2 hrs, TLC shows completion. Workup done with 5% citric acid,

saturated NaHCO$_3$, then dry with brine and MgSO$_4$. The reaction mixture was concentrated

25   and chromatographed on a Monster Pipette column in 1:1 hexane: EtOAc then 7:3 hexane:

EtOAc to avail compound 19 (28 mg , 67%) ^{1}H NMR (CDCl$_3$): δ 7.37 (d, 2H), 7.20 (m,

15H), 6.90 (d, 2H), 5.07-4.93 (m, 4H), 4.16 (brs, 1H), 3.80 (s, 3H), 3.75-3.37 (m, 4H), 3.36

(d, 1H), 3.20-2.93 (m, 6H), 2.80- 2.75 (dd, 1H).

Example 14

30

Compound 19 (28 mg, 0.35 mmol) was stirred in 4 mL DCM with addition of 1 mL TFA.

Stir for 45 minutes, at which time complete deprotection was noted by TLC as well as MS.

Azeotrope with toluene. The residue was dissolved in 1 mL CH$_3$CN, cooled to 0°C. Bis-

Furan *para*-Nitro phenol carbonate 11 (12 mg, 0.038 mmol), dimethyl amino pyridine (~ 1 mg, 0.008 mmol) and diisopropylethylamine (0.018 mL, 0.103 mmol) were added. The mixture was stirred and allowed to come to room temperature and stirred until TLC in 1:1 hexane:EtOAc showed completion. The reaction mixture was concentrated and the residue

5 was partitioned between saturated NaHCO$_3$ and EtOAc. The organic layer was dried with brine and MgSO$_4$, then chromatographed on silica with hexane:EtOAc to afford compound 20 (20 mg, 67%). ^{1}NMR (CDCl$_3$): δ 7.76 (d, 2H), 7.34–7.16 (m, 15 H), 7.07 (d, 2H), 5.56 (d, 1H), 5.09 (m, 4H), 4.87 (m, 1H), 4.01 (m, 1H), 3.91 (m, 2H), 3.87 (s, 3H), 3.86 (m, 1H), 3.69 (m, 1H), 3.67 (m, 1H) 3.60 (d, 2H) 3.28 (m, 1H) 3.25 (d, 2H), 3.32 (d, 1H), 3.13 (m, 1H),

10 3.02 (m, 1H) 2.85 (d, 1H), 2.83 (m, 1H) 2.52 (m, 1H) 1.47 (m, 1H), 1.31 (m, 1H) 0.98 (s, 3H), 0.95 (s,3H).

Example 15

Compound 20 (7 mg, 0.008 mmol) was treated in a manner identical to example 8 to afford

15 compound 21 (5 mg, 90%) ^{1}H NMR (CDCl$_3$): δ 7.80 (d, 2H), 7.25–7.16 (m, 5H), 7.09 (d, 2H), 5.58 (d, 1H), 4.92 (m, 1H), 3.99 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.86 (m, 1H), 3.77 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.71 (m, 1H) 3.71 (m, 1H), 3.68 (m, 1H), 3.57 (d,1H), 3.41 (d, 1H), 3.36 (m, 1H), 3.29 (d, 1H), 3.25 (d, 2H), 3.18 (m, 1H), 3.12 (m, 1H), 3.01 (d, 1H) 2.86 (m, 1H), 2.53 (m, 1H) 1.50 (m, 1H), 1.33 (m, 1H), 1.02 (s, 3H), 0.99 (s,

20 3H).

Example 16

Compound 15 (1.86 g, 9.20 mmol) was treated with triflate 22 in a manner identical to example 10 to afford compound 23 (0.71 g, 21.8%) ^{1}H NMR (CDCl$_3$): δ 5.21 (brs, 1H) 4.16–

25 4.07 (m, 4H), 3.71-3.69 (d, 2H), 3.24 (s, 2H), 1.43 (s, 9H), 1.34-1.28 (m, 6H) 0.86 (s, 6H).

Example 17

Compound 23 (151 mg, 0.427 mmol) was dissolved in 10 mL DCM and 1.0 mL TFA was added. The reaction was stirred until completion. The reaction was azeotroped with toluene

30 and the residue was then dissolved in THF and treated with basic Dowex resin beads. Afterwards, the beads were filtered away and solvent was removed to avail compound 24 (100 mg, 92%) ^{1}H NMR (CDCl$_3$): δ 4.15-4.05 (m, 4H), 3.72-3.69 (d, 2H), 3.27 (s, 2H), 1.30-1.26 (m, 6H) 0.81 (s, 6H).

Example 18

Compound 24 (100 mg, 0.395 mmol) was treated in a manner identical to example 12 to avail compound 25 (123 mg, 60%). ^{1}H NMR (CDCl$_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H)

5   4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 19

Compound 25 (88 mg, 0.171 mmol) was treated in a manner identical to example 13 to afford

10   compound 26 (65 mg, 55%) ^{1}H NMR (CDCl$_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H) 4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 20

15   Compound 26 (65 mg, 0.171 mmol) was treated in a manner identical to example 14 to afford compound 27 (49 mg, 70%) ^{1}H NMR:

(CDCl$_3$):δ 7.75 (d, 2H), 7.25–7.24 (m,4 H), 7.18 (m, 1H) 6.99 (d, 2H), 5.63 (d, 1H), 5.01 (m, 1H), 4.16 (m, 4H), 3.94 (m, 1H), 3.88 (m, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 3.81 (m, 1H), 3.74 (m, 2H),), 3.70 (m, 1H), 3.69 (m, 1H) 3.43 (m, 1H), 3.24 (m, 1H), 3.22 (m, 2H) 3.21 (m,

20   2H) 3.12 (m, 1H), 3.02 (m, 1H) 2.86 (m, 1H), 2.72 (m, 1H), 1.54 (m, 1H), 1.38 (m, 1H) 1.35 (m, 6H) 1.00 (s, 3H), 0.96 (s,3H).

Example 21

Boc protected amine 28 (103 mg, 0.153 mmol) was dissolved in DCM (5 mL). The stirred

25   solution was cooled to 0°C. BBr$_3$ as a 1.0 M solution in DCM (0.92 mL, 0.92 mmol) was added dropwise over 10 min, and the reaction was allowed to continue stirring at 0°C for 20 min. The reaction was warmed to room temperature and stirring was continued for 2 hours. The reaction was then cooled to 0°C and quenched by dropwise addition of MeOH (1 mL). The reaction mixture was evaporated and the residue suspended in methanol which was

30   removed under reduced pressure. The procedure was repeated for EtOAc and finally toluene to afford free amine HBr salt 29 (107 mg, >100%) which was used without further purification.

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Example 22

Amine HBr salt 29 (50 mg, 0.102 mmol) was suspended in 2 mL CH3CN with stirring then
cooled to 0°C. DMAP (25 mg, 0.205 mmol) was added, followed by Carbonate11. The
reaction was stirred at 0°C for 1.5 hrs then allowed to warm to room temperature. The

5   reaction was stirred overnight. A few drops Acetic acid were added to the reaction mixture,
which was concentrated and re-diluted with ethyl acetate, shaken with 10% citric acid then
saturated NaHCO3. The organic layer was dried with brine and MgSO4 and eluted on silica to
afford di-phenol 30 (16 mg, 28%) ^{1}H NMR (CD3OD): δ 7.61, (d, 2H), 7.01 (d, 2H), 6.87 (d,
2H), 6.62 (d, 2H), 5.55 (d, 1H), 4.93 (m, 1H), 3.92 (m, 2H), 3.79 (m, 5H), 3.35 (m, 1H), 3.07

10 (m, 2H), 2.88 (m, 3H), 2.41 (m, 1H), 2.00 (m, 1H), 1.54 (m, 1H), 1.31 (dd, 1H) 0.89-0.82
(dd, 6H).

Example 23

A solution of di-phenol 30 (100 mg, 0.177 mmol) was made in CH3CN that had been dried

15 over K2CO3. To this, the triflate (0.084 mL, 0.23 mmol) was added, followed by Cs2CO3
(173 mg, 0.531 mmol). The reaction was stirred for 1 hr. TLC (5% IprOH/DCM) showed 2
spots with no starting materials left. Solvent was evaporated and the residue was partitioned
between EtOAc and water. The organic layer was washed with saturated NaHCO3, then
dried with brine and MgSO4. The mixture was separated by column chromatography on

20 silica with 3% IprOH in DCM. The upper spot 31 (90 mg, 46%) was confirmed to be the *bis*
alkylation product. The lower spot required further purification on silica gel plates to afford a
single *mono* alkylation product 32 (37 mg, 26%). The other possible alkylation product was
not observed. NMR : ^{1}H NMR (CDCl3): *for 31:* δ 7.57 (d, 2H), 7.37 (m, 10H) 7.03 (d,
2H), 6.99 (d, 2H), 6.73 (d, 2H), 5.69 (d, 1H), 5.15-5.09 (m, 4H), 5.10 (m, 1H), 4.32 (d, 2H),

25 4.02 (d, 1H), 3.82 (m, 1H) 3.81 (m, 1H), 3.93-3.81 (m, 2H), 3.74 (d, 1H), 3.06 (m, 1H), 3.00
(m, 1H), 2.96 (m, 1H), 2.91 (m, 1H) 2.77 (m, 1H) 2.64 (m, 1H) 2.47 (m, 1H) 1.82 (m, 2H)
1.79 (m, 1H), 0.94-0.86 (dd, 6H) *for 32:* δ 7.68 (d, 2H), 7.33-7.35 (m, 20H), 7.11 (d, 2H),
6.96 (d, 2H), 6.80 (d, 2H), 5.26 (d, 1H), 5.11(m, 8H), 5.00 (m, 1H) 4.23 (d, 2H), 4.19 (d,
2H), 3.93 (m, 1H), 3.82-3.83 (m, 3H), 3.68-3.69 (m, 2H) 3.12-2.75 (m, 7H), 1.82 (m, 1H),

30 1.62-1.52 (d, 2H), 0.89-0.86 (dd, 6H).

Example 24

Ref: J. Med. Chem. 1992, 35 10,1681-1701

To a solution of phosphonate 32 (100 mg, 0.119 mmol) in dry dioxane was added Cs₂CO₃ (233 mg, 0.715 mmol), followed by 2-(dimethylamino) ethyl chloride hydrochloride salt (69 mg, 0.48 mmol). The reaction was stirred at room temperature and monitored by TLC. When it was determined that starting material remained, additional Cs₂CO₃ (233 mg, 0.715

5   mmol) as well as amine salt (69 mg, 0.48 mmol) were added and the reaction was stirred overnight at 60°C. In the morning when TLC showed completion the reaction was cooled to room temperature, filtered, and concentrated. The product amine 33 (40 mg, 37%) was purified on silica. Decomposition was noted as lower spots were seen to emerge with time using 15% MeOH in DCM on silica.

10

Example 25:

Amine 33 (19 mg, 0.021 mmol) was dissolved in 1.5 mL DCM. This solution was stirred in an icebath. Methane sulfonic acid (0.0015 mL, 0.023 mmol) was added and the reaction was stirred for 20 minutes. The reaction was warmed to room temperature and stirred for 1 hour.

15   The product, amine mesylate salt 34 (20 mg, 95%) was precipitated out by addition of hexane. ^{1}H NMR (CD₃OD): δ 7.69 (d, 2H), 7.35 (m, 10H), 7.15 (m, 4H) 6.85 (m, 2H), 5.49 (d, 1H), 5.10 (m, 4H), 4.83 (m, 1H), 4.62 (d, 2H), 4.22 (m, 2H), 3.82 (m, 1H), 3.56 (m, 1H), 3.48 (m, 2H), 3.35 (m, 1H), 2.99 (m, 1H), 2.95 (m, 1H), 2.84 (s, 6H), 2.78 (m, 1H), 2.75 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H) 1.94 (m, 1H), 1,43 (m, 1H), 1.27 (m, 1H), 0.77 (dd, 6H).

Example Section E

Scheme 1
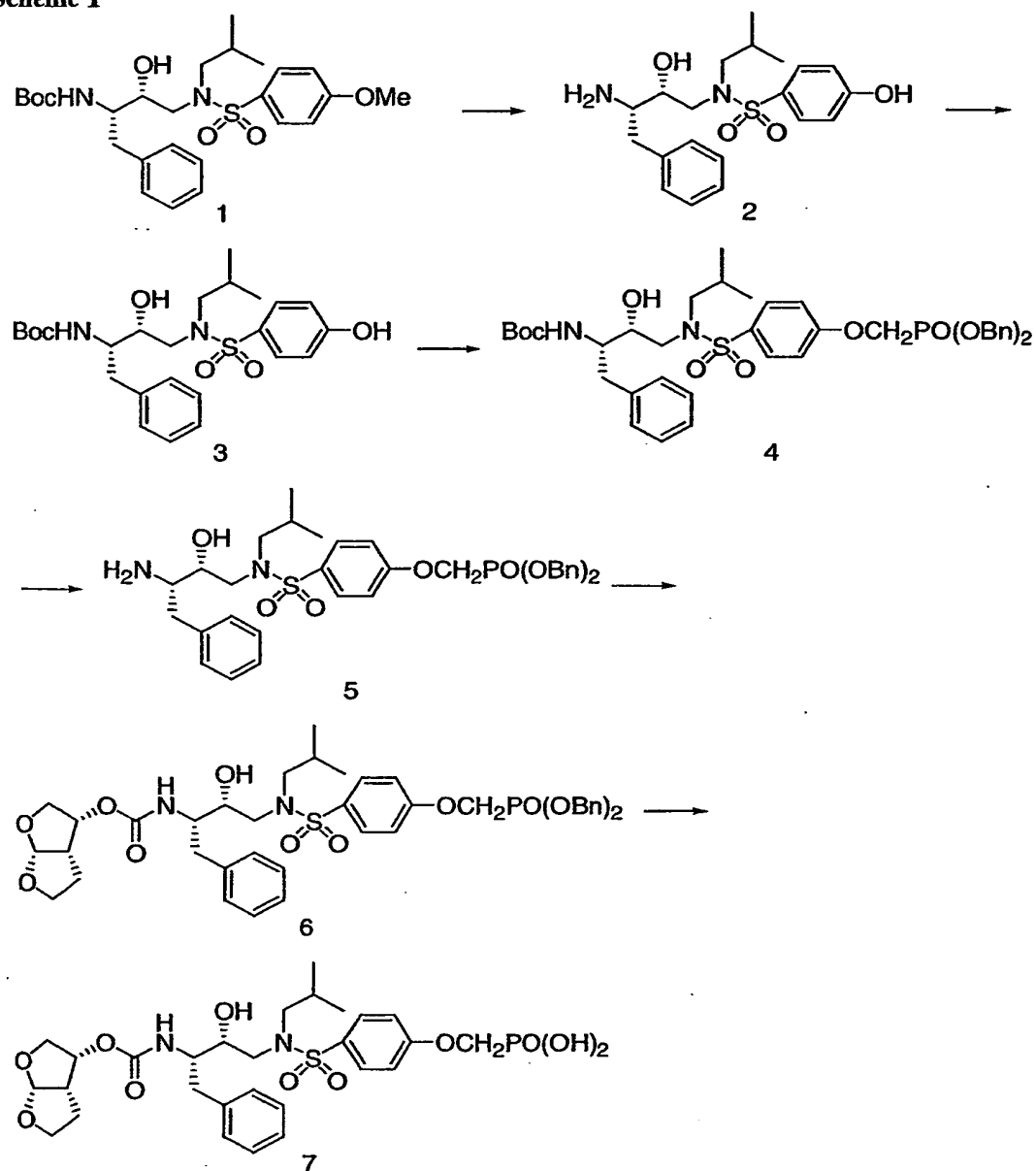
Example 1

To a solution of phenol 3 (336 mg, 0.68 mmol) in THF (10 mL) was added Cs_2CO_3 (717 mg, 2.2 mmol) and triflate (636 mg, 1.5 mmol) in THF (3 mL). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and

5   water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 40-50% EtOAc/hexane) to give dibenzylphosphonate 4 (420 mg, 80%) as a colorless oil.

Example 2

10
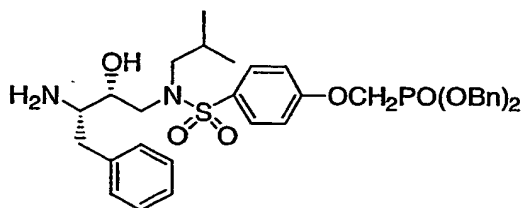
To a solution of dibenzylphosphonate 4 (420 mg, 0.548 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.21 mL, 2.74 mmol). After the reaction mixture was stirred for 2 h at room temperature, additional TFA (0.84 mL, 11 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was evaporated under reduced pressure and the residue was

15   partitioned between EtOAc and 1M $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give amine 5 (325 mg, 89%).

Example 3
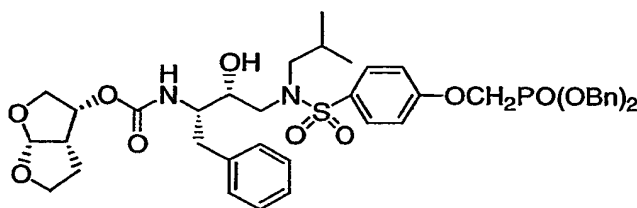
20   To a solution of carbonate (79 mg, 0.27 mmol), amine 5 (178 mg, 0.27 mmol), and CH_3CN (10 mL) was added DMAP (66 mg, 0.54 mmol) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 16 hours, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 60-90% EtOAc/hexane) to give a mixture of carbamate 6 and starting carbonate. The mixture was

25   further purified by HPLC on C18 reverse phase chromatography (eluting 60% CH_3CN/water)

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to give carbamate **6** (49 mg, 22%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, 2H), 7.22 (m, 15 H), 6.95 (d, 2H), 5.62 (d, 1H), 5.15 (dt, 4H), 5.00 (m, 2H), 4.21 (d, 2H), 3.88 (m, 4H), 3.67 (m, 3H), 3.15 (m, 2H), 2.98 (m, 3H), 2.80 (m, 2H), 1.82 (m, 1H), 1.61 (m, 1H), 0.93 (d, 3H), 0.88 (d, 3H).

5

Example 4
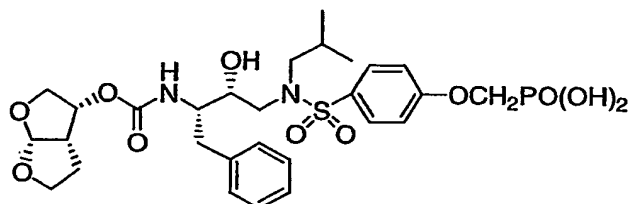
To a solution of carbamate **6** (21 mg, 0.026 mmol) in EtOH / EtOAc (2 mL/1 mL) was added 10% Pd/C (11 mg). After the reaction mixture was stirred under H$_2$ atmosphere (balloon) for 10   2 hours, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give phosphonic acid **7** (17 mg, 100%) as a colorless solid. ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.73 (d, 2H), 7.19 (m, 5H), 7.13 (d, 2H), 5.53 (d, 1H), 4.26 (d, 2H), 3.86 (m, 1H), 3.64 (m, 5H), 3.38 (d, 1H), 3.13 (d, 1H), 3.03 (dd, 1H), 2.86 (m, 3H), 2.48 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.28 (m, 2H), 1.13 (t, 1H), 0.88 (d, 3H), 0.83 (d, 3H).

Scheme 2

8

9
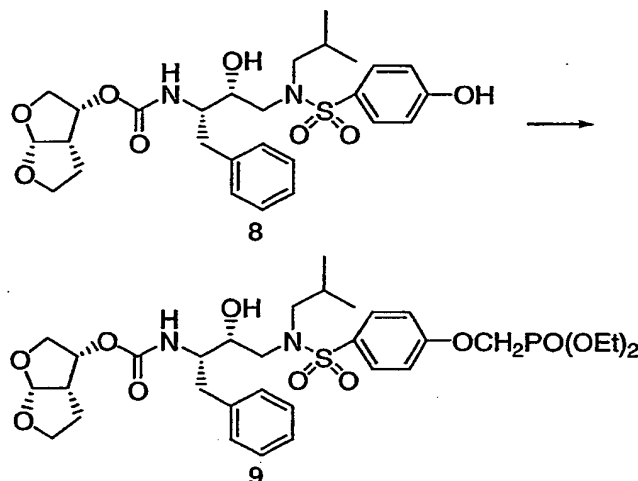
Example 5

5
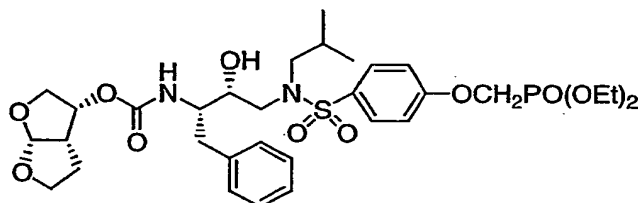
To a solution of phenol **8** (20 mg, 0.036 mmol) and triflate (22 mg, 0.073 mmol) in THF (2

mL) was added Cs_2CO_3 (29 mg, 0.090 mmol). After the reaction mixture was stirred for 30

min at room temperature, the mixture was partitioned between EtOAc and water. The

10   organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The

crude product was purified by preparative thin layer chromatography (eluting 80%

EtOAc/hexane) to give diethylphosphonate **9** (21 mg, 83%) as a colorless oil. ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.73 (d, 2H), 7.25 (m, 5H), 7.07 (d, 2H), 5.64 (d, 1H), 5.01 (m, 2H), 4.25 (m,

6H), 3.88 (m, 4H), 3.70 (m, 3H), 2.97 (m, 6H), 1.70 (m, 4H), 1.38 (t, 6H), 0.92 (d, 3H), 0.88

15   (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 18.1.

Scheme 3
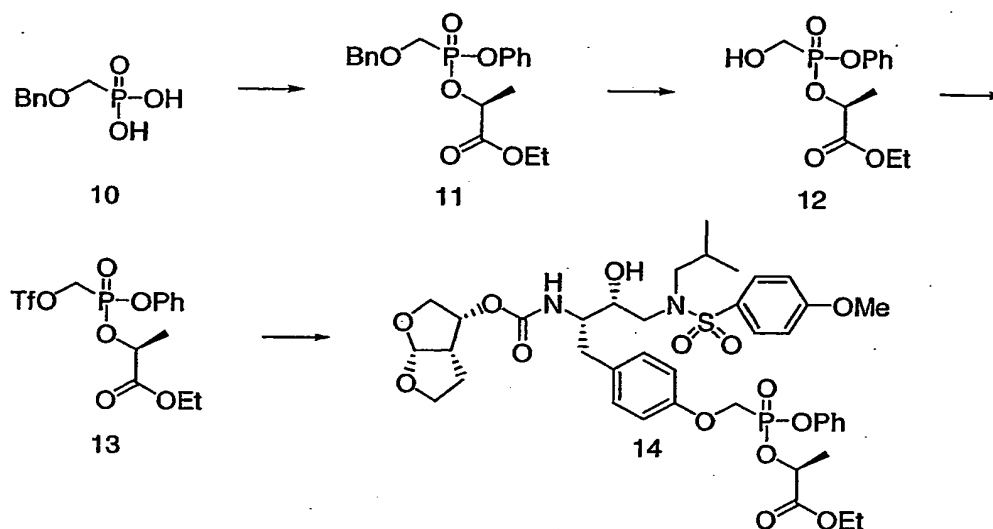
Example 6
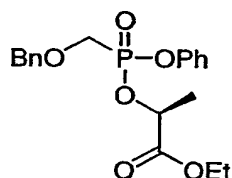
To a solution of phosphonic acid **10** (520 mg, 2.57 mmol) in CH$_3$CN (5 mL) was added thionyl chloride (0.75 mL, 10.3 mmol) and heated to 70°C in an oil bath. After the reaction mixture was stirred for 2 h at 70°C, the mixture was concentrated and azeotroped with toluene. To a solution of the crude chloridate in toluene (5 mL) was added tetrazole (18 mg, 0.26 mmol) at 0°C. To this mixture was added phenol (121 mg, 1.28 mmol) and triethylamine (0.18 mL, 1.28 mmol) in toluene (3 mL) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 2 h, ethyl lactate (0.29 mL, 2.57 mmol) and triethylamine (0.36 mL, 2.57 mmol) in toluene (2.5 mL) were added. The reaction mixture was stirred for 16 hours at room temperature, at which time the mixture was partitioned between EtOAc and sat. NH$_4$Cl. The organic phase was washed with sat. NH$_4$Cl, 1M NaHCO$_3$, and brine, then dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 20-40% EtOAc/hexane) to give two diastereomers of phosphonate **11** (66 mg, 109 mg, 18% total) as colorless oils.

Example 7A

$$HO\!-\!CH_2\!-\!\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{P}}}\!-\!OPh$$
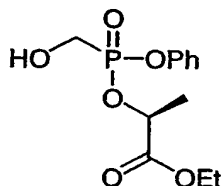
To a solution of phosphonate **11** isomer A (66 mg, 0.174 mmol) in EtOH (2 mL) was added

5   10% Pd/C (13 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for
6 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced
pressure to give alcohol **12** isomer A (49 mg, 98%) as a colorless oil.

Example 7B

10 To a solution of phosphonate **11** isomer B (110 mg, 0.291 mmol) in EtOH (3 mL) was added
10% Pd/C (22 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for
6 h, it was filtered through Celite. The filtrate was evaporated under reduced pressure to give
alcohol **12** isomer B (80 mg, 95%) as a colorless oil.

15 Example 8A

$$TfO\!-\!CH_2\!-\!\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{P}}}\!-\!OPh$$
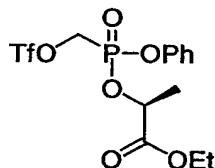
To a solution of alcohol **12** isomer A (48 mg, 0.167 mmol) in CH_2Cl_2 (2 mL) was added 2,6-
lutidine (0.03 mL, 0.250 mmol) and trifluoromethanesulfonic anhydride (0.04 mL, 0.217

20 mmol) at -40°C (dry ice-CH$_3$CN bath). After the reaction mixture was stirred for 15 min at -
40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The
organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and
evaporated under reduced pressure to give triflate **13** isomer A (70 mg, 100%) as a pale
yellow oil.

25

Example 8B

To a solution of alcohol **12** isomer B (80 mg, 0.278 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (0.05 mL, 0.417 mmol) and trifluoromethanesulfonic anhydride (0.06 mL, 0.361 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **13** isomer B (115 mg, 98%) as a pale yellow oil.

Example 9A
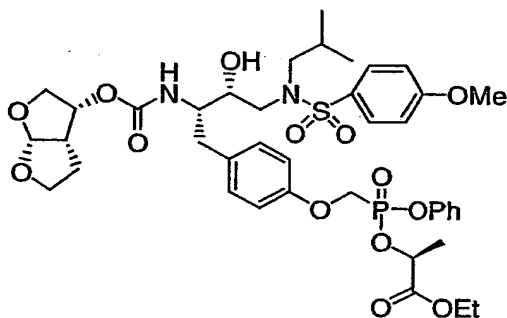
To a solution of phenol (64 mg, 0.111 mmol):
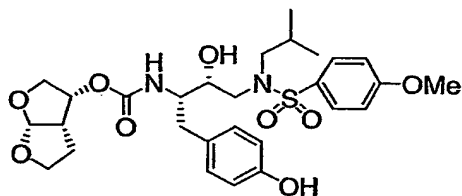
and triflate **13** isomer A (70 mg, 0.167 mmol) in THF (2 mL) was added Cs_2CO_3 (72 mg, 0.222 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH_3CN/water) to give phosphonate **14** isomer A (30 mg, 32%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 7.00 (m, 5H), 5.65 (d, 1H), 5.14 (m, 1H), 5.00 (m, 2H), 4.54 (dd, 1H), 4.44 (dd, 1H), 4.17 (m, 2H), 3.96 (dd, 1H), 3.86 (m, 5H), 3.72

(m, 3H), 3.14 (m, 1H), 2.97 (m, 4H), 2.79 (m, 2H), 1.83 (m, 1H), 1.62 (m, 3H), 1.50 (d, 3H), 1.25 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 17.4.

<u>Example 9B</u>

To a solution of phenol (106 mg, 0.183 mmol):
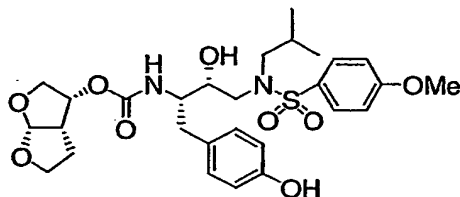
and triflate 13 isomer B (115 mg, 0.274 mmol) in THF (2 mL) was added Cs$_2$CO$_3$ (119 mg, 0.366 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH$_3$CN/water) to give phosphonate 14 isomer B (28 mg, 18%) as a colorless solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 6.94 (m, 5H), 5.66 (d, 1H), 5.17 (m, 1H), 4.99 (m, 2H), 4.55 (m, 1H), 4.42 (m, 1H), 4.16 (m, 2H), 3.97 (m, 1H), 3.85 (m, 5H), 3.72 (m, 3H), 3.13 (m, 1H), 2.97 (m, 4H), 2.80 (m, 2H), 1.83 (m, 1H), 1.60 (m, 6H), 1.22 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 15.3.

Resolution of Compound 14 Diastereomers

Analysis was performed on an analytical Alltech Econosil column, conditions described below, with a total of about 0.5 mg 14 injected onto the column. This lot was a mixture of major and minor diastereomers where the lactate ester carbon is a mix of R and S configurations. Up to 2 mg could be resolved on the analytical column. Larger scale injections (up to 50 mg 14) were performed on an Alltech Econosil semi-preparative column, conditions described below.

The isolated diastereomer fractions were stripped to dryness on a rotary evaporator under house vacuum, followed by a final high vacuum strip on a vacuum pump. The

chromatographic solvents were displaced by two portions of dichloromethane before the final high vacuum strip to aid in removal of trace solvents, and to yield a friable foam.

5   The bulk of the diastereomer resolution was performed with *n*-heptane substituted for hexanes for safety considerations.

Sample Dissolution: While a fairly polar solvent mixture is described below, the sample may be dissolved in mobile phase with a minimal quantity of ethyl alcohol added to dissolve the sample.

10

Analytical Column, 0.45 mg Injection, Hexanes – IPA (90:10)
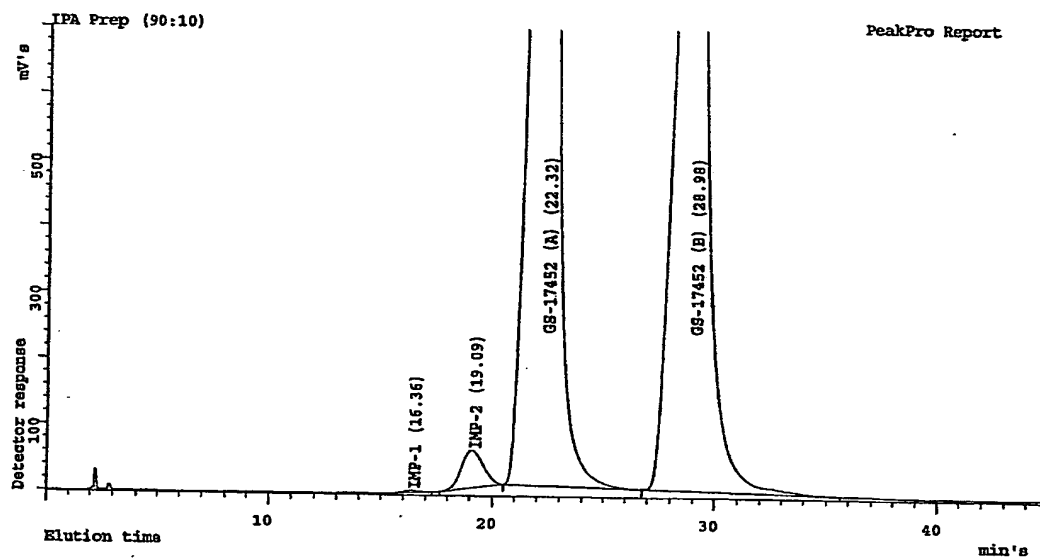
HPLC CONDITIONS

Column	: Alltech Econosil, 5 µm, 4.6 x 250 mm
Mobile Phase	: Hexanes – Isopropyl Alcohol (90:10)
Flow Rate	: 1.5 mL/min
Run Time	: 50 min
Detection	: UV at 242 nm
Temperature	: Ambient
Injection Size	: 100 µL
Sample Prep.	: ~ 5 mg/mL, dissolved in hexanes – ethyl alcohol (75:25)
Retention Times	: **14 ~ 22** min
	: **14 ~ 29** min
	: Less Polar Impurity ~ 19 min

Semi-Preparative Column, 50 mg Injection, *n*-Heptane – IPA (84:16)
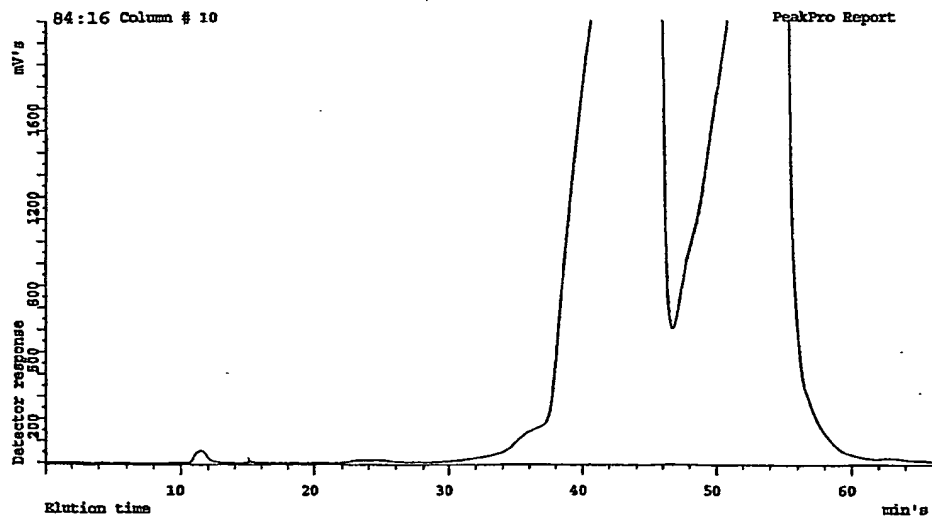
HPLC CONDITIONS

Column   : Alltech Econosil, 10 µm, 22 x 250 mm

Mobile Phase   : *n*-Heptane – Isopropyl Alcohol (84:16)

Flow Rate   : 10 mL/min

Run Time   : 65 min

Detection   : UV at 257 nm

Temperature   : Ambient

Injection Size   : ~50 mg

Dissolution   : 2 mL mobile phase plus ~ 0.75 mL ethyl alcohol

Retention Times   : **14 ~ 41** min

                    : **14 ~ 54** min

                    : Less Polar Impurity ~ Not resolved

Example Section F

Example 1

Phosphonic acid 2: To a solution of compound 1 (A. Flohr et al, J. Med. Chem., 42, 12,

5 1999; 2633-2640) (4.45 g, 17 mmol) in CH_2Cl_2 (50 mL) at room temperature was added bromotrimethylsilane (1.16 mL, 98.6 mmol). The solution was stirred for 19 h. The volatiles were evaporated under reduced pressure to give the oily phosphonic acid 2 (3.44 g, 100%). ^1H NMR (CDCl$_3$) δ 7.30 (m, 5H), 4.61 (s, 2 H), 3.69 (d, 2H).

10 ### Example 2

Compound 3: To a solution of phosphonic acid 2 (0.67 g, 3.3 mmol) in CH_3CN (5 mL) was added thionyl chloride (1 mL, 13.7 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH_2Cl_2 (20 mL) and

15 cooled in an ice/water bath. Ethyl lactate (1.5 mL, 13.2 mmol) and triethyl amine (1.8 mL, 13.2 mmol) were added dropwise. The mixture was stirred for 4 h at room temperature and dilluted with more CH_2Cl_2 (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous NaHCO$_3$, and brine, dried (MgSO$_4$) filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 3

20 (0.548 g, 41%). ^1H NMR (CDCl$_3$) δ 7.30 (m, 5H), 5.00-5.20 (m, 2H), 4.65 (m, 2H), 4.20 (m, 4H), 3.90 (d, 2H), 1.52 (t, 6H), 1.20 (t, 6H).

Example 3

Alcohol 4: A solution of compound 3 (0.54 g, 1.34 mmol) in EtOH (15 mL) was treated with

25 10% Pd/C (0.1 g) under H_2 (100 psi) for 4 h. The mixture was filtered and the filtrate was treated with fresh 10% PD/C (0.1 g) under H_2 (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 4 (0.395 g, 94%) as an oil. ^1H NMR (CDCl$_3$) δ 4.90-5.17 (m, 2H), 4.65 (q, 2H), 4.22 (m, 4H), 4.01 (m, 2H), 1.55 (t, 6H), 1.21 (t, 6H); ^{31}P NMR (CDCl$_3$) δ 22.8.

30 ### Example 4

Triflate 5: To a solution of alcohol 4 (122.8 mg, 0.393 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.069 mL, 0.59 mmol) and trifluoromethansulfonic anhydride

(0.086 mL, 0.51 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH₂Cl₂ and saturated NaHCO₃. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product 5 (150 mg, 87%) was used for the next step without further purification. ¹H NMR (CDCl₃) δ

5   5.0-5.20 (m, 2H), 4.93 (d, 2H), 4.22 (m, 4H), 1.59 (m, 6H), 1.29 (t, 6H).

Example 5

Phosphonate 6: A solution of phenol 8 (see Scheme Section A, Scheme 1 and 2) (32 mg, 0.055 mmol) and triflate 5 (50 mg, 0.11 mmol) in THF (1.5 mL) at room temperature was

10   treated with Cs₂CO₃ (45.6 mg, 0.14 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated NaHCO₃. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the phosphonate 6 (41 mg, 84%) as a solid. ¹H NMR (CDCl₃) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00

15   (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 4.90-5.22 (m, 3H), 4.40 (m, 2H), 4.20 (m, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 12H), 1.25 (m, 6H), 0.85-0.90 (m, 6H); ³¹P NMR (CDCl₃) δ 20.0.

Example 6

20   Compound 7: To a solution of phosphonic acid 2 (0.48 g, 2.37 mmol) in CH₃CN (4 mL) was added thionyl chloride (0.65 mL, 9.48 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH₂Cl₂ (5 mL) and cooled in an ice/water bath. Ethyl glycolate (0.9 mL, 9.5 mmol) and triethyl amine (1.3 mL, 9.5

25   mmol) were added dropwise. The mixture was stirred for 2 h at room temperature and dilluted with more CH₂Cl₂ (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous NaHCO₃, and saturated NaCl, dried (MgSO₄) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 7 (0.223 g, 27%). ¹H NMR (CDCl₃) δ 7.30 (m, 5H), 4.65 (m, 6H), 4.25 (q, 4H), 3.96 (d, 2H),

30   1.27 (t, 6H); ³¹P NMR (CDCl₃) δ 24.0.

Example 7

Alcohol 8: A solution of compound 7 (0.22 g, 0.65 mmol) in EtOH (8 mL) was treated with 10% Pd/C (0.04 g) under H_2 (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 8 (0.156 g, 96%) as an oil. ^1H NMR ($CDCl_3$) δ 4.66 (m, 4H), 4.23 (q, 4H), 4.06 (d, 2H), 1.55 (t, 6H), 1.26 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 26.8.

5

Example 8

Triflate 9: To a solution of alcohol 8 (156 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.11 mL, 0.93 mmol) and trifluoromethansulfonic anhydride (0.136 mL, 0.8 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH_2Cl_2 and

10 saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product 9 (210 mg, 88%) was used for the next step without further purification. ^1H NMR ($CDCl_3$) δ 4.90 (d, 2H), 4.76 (d, 4H), 4.27 (q, 4H), 1.30 (t, 6H).

15 Example 9

Phosphonate 10: A solution of phenol 8 (30 mg, 0.052 mmol) and triflate 9 (30 mg, 0.078 mmol) in THF (1.5 mL) at room temperature was treated with Cs_2CO_3 (34 mg, 0.1 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and

20 evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the unreacted phenol (xx) (12 mg, 40%) and the phosphonate 10 (16.6 mg, 38%) as a solid. ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 5.00 (m, 2H), 4.75 (m, 4H), 4.48 (d, 2H), 4.23 (q, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 2.23 (b.s., 2H), 1.52-1.87 (m, 4H),

25 1.25 (t, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 22.0.

Example 10

Compound 11: To a solution of phosphonic acid 2 (0.512 g, 2.533 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.74 mL, 10 mmol) and the solution was heated at 70°C for 2.5

30 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in toluene (8 mL) and cooled in an ice/water bath. A catalytic amount of tetrazol (16 mg, 0.21 mmol) was added followed by the addition of a solution of triethylamine (0.35 mL, 2.53 mmol) and phenol (238

mg, 2.53 mmol) in toluene (5 mL). The mixture was stirred at room temperature for 3 h. A solution of ethyl glycolate (0.36 mL, 3.8 mmol) and triethyl amine (0.53 mL, 3.8 mmol) in toluent (3 mL) was added dropwise. The mixture was stirred for 18 h at room temperature and partitioned in EtOAc and 0.1N HCl. The organic solution was washed with saturated

5   aqueous NaHCO₃, and saturated NaCl, dried (MgSO₄) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford diphenyl phophonate as a byproduct (130 mg) and compound 11 (0.16 g, 18%). ^{1}H NMR (CDCl₃) δ 7.15-7.40 (m, 10H), 4.58-4.83 (m, 4H), 4.22 (q, 2H), 4.04 (dd, 2H), 1.24 (t, 3H).

10   Example 11

Alcohol 12: A solution of compound 11 (0.16 g, 0.44 mmol) in EtOH (5 mL) was treated with 10% Pd/C (0.036 g) under H₂ (1 atmosphere) for 22 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 12 (0.112 g, 93%) as an oil. ^{1}H NMR (CDCl₃) δ 7.15-7.36 (m, 5H), 4.81 (dd, 1H), 4.55 (dd, 1H), 4.22 (q, 2H), 4.12 (m, 2H), 3.78 (b.s., 1H),

15   1.26 (t, 6H); ^{31}P NMR (CDCl₃) δ 22.9

Example 12

Triflate 13: To a solution of alcohol 12 (112 mg, 0.41 mmol) in CH₂Cl₂ (5 mL) at -40°C were added 2,6-lutidine (0.072 mL, 0.62 mmol) and trifluoromethansulfonic anhydride (0.09

20   mL, 0.53 mmol). Stirring was continued at 0°C for 3 h. and the mixture partitioned in CH₂Cl₂ and saturated NaHCO₃. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30% EtOAc/hexane) affording triflate 13 (106 mg, 64%). ^{1}H NMR (CDCl₃) δ 7.36 (m, 2H), 7.25 (m, 3H), 4.80-5.10 (m, 3H), 4.60 (dd, 1H),

25   4.27 (q, 2H), 1.28 (t, 3H); ^{31}P NMR (CDCl₃) δ 11.1

Example 13

Phosphonate 14: A solution of phenol 8 (32 mg, 0.052 mmol) and triflate 13 (32 mg, 0.079 mmol) in CH₃CN (1.5 mL) at room temperature was treated with Cs₂CO₃ (34 mg, 0.1 mmol).

30   The mixture was stirred for 1 h and partitioned in EtOAc and saturated NaHCO₃. The organic layer was washed with saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (70%

EtOAc/hexane) affording phosphonate 14 (18 mg, 40%). ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 6.75-7.35 (m, 11H, 5.65 (d, 1H), 5.00 (m, 2H); 4.50-4.88 (m, 3H), 4.20 (q, 2H), 3.84 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 6H), 1.25 (t, 3H), 0.85-0.90 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.9, 17.7.

5

Example 14

Piperidine 16: A solution of compound 15 (3.1 g, 3.673 mmol) in MeOH (100 mL) was treated with 10% Pd/C (0.35 g) under H$_2$ (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford phenol 16 (2 g, 88%). ^{1}H NMR (CD$_3$OD) δ 7.76 (d, 10 2H), 7.08 (d, 2H), 7.04 (d, 2H), 6.65 (d, 2H), 5.59 (d, 1H), 4.95 (m, 1H), 3.98 (s, 3H), 3.65-4.00 (m, 5H), 3.30-3.50 (m, 3H), 2.80-3.26 (m, 5H), 2.40-2.70 (m, 3H), 1.35-2.00 (m, 7H), 1.16 (m, 2H); MS (ESI) 620 (M+H).

Example 15

15 Formamide 17: Piperidine 16 obtained above (193 mg, 0.3118 mmol) in DMF (4 mL) was treated with formic acid (0.035 mL, 0.936 mmol), triethylamine (0.173 mL, 1.25 mmol) and EDCI (179 mg, 0.936 mmol) at room temperature. The mixture was stirred for 18 h and partitioned in EtOAc and saturated NaHCO$_3$. The organic layer was washed with saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product 20 was purified by chromatography on silica gel (EtOAC/hexane) affording formamide 17 (162 mg, 80%). ^{1}H NMR (CDCl$_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.97 (d, 2H), 6.76 (d, 2H), 5.63 (d, 1H), 5.37 (bs, 1H), 5.04 (m, 1H), 4.36 (m, 1H), 3.93 (s, 3H), 3.52-3.95 (m, 7H), 2.70-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H).

25 Example 16

Dibenzyl phosphonate 18: A solution of phenol 17 (123 mg, 0.19 mmol) and dibenzyl trifluoromethansulfonyloxymethanphosphonate YY (120 mg, 0.28 mmol) in CH$_3$CN (1.5 mL) at room temperature was treated Cs$_2$CO$_3$ (124 mg, 0.38 mmol). The mixture was stirred for 3 h and partitioned in CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was washed with 30 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH$_2$Cl$_2$) affording phosphonate 18 (154 mg, 88%). ^{1}H NMR (CDCl$_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.35 (m, 10H), 7.10 (d, 2H), 6.97 (d, 2H), 6.80 (d, 2H), 5.63 (d, 1H), 4.96-5.24 (m, 6H), 4.37

(m, 1H), 4.20 (d, 2H), 3.84 (s, 3H), 3.52-3.95 (m, 7H), 2.55-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H). ^{31}P NMR (CDCl$_3$) δ 20.3.

Example 17

5   Phosphonic acid 19: A solution of phosphonate 18 (24 mg, 0.026 mmol) in MeOH (3 mL) was treated with 10% Pd/C (5 mg) under H$_2$ (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford phosphonic acid 19 as a solid (18 mg, 93%). ^{1}H NMR (CD$_3$OD) δ 8.00 (s, 1H), 7.67 (d, 2H), 7.18 (d, 2H), 7.09 (d, 2H), 6.90 (d, 2H), 5.60 (d, 1H), 4.30 (m, 1H), 4.16 (d, 2H), 3.88 (s, 3H), 3.60-4.00 (m, 7H), 3.04-3.58 (m, 5H), 2.44-

10   2.92 (m, 5H), 1.28-2.15 (m, 5H), 1.08 (m, 2H). ^{31}P NMR (CDCl$_3$) δ 16.3.

Example 18

Diethyl phosphonate 20: A solution of phenol 17 (66 mg, 0.1 mmol) and diethyl trifluoromethansulfonyloxymethanphosphonate XY (46 mg, 0.15mmol) in CH$_3$CN (1.5 mL) at

15   room temperature was treated Cs$_2$CO$_3$ (66 mg, 0.2 mmol). The mixture was stirred for 3 h and partitioned in CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH$_2$Cl$_2$) affording the unreacted 17 (17 mg, 26%) and diethyl phosphonate 20 (24.5 mg, 41%). ^{1}H NMR (CDCl$_3$) δ

20   8.00 (s, 1H), 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88 (d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.39 (m, 1H), 4.24 (m, 5H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.55-3.16 (m, 8H), 1.50-2.00 (m, 7H), 1.36 (t, 6H), 1.08 (m, 2H). ^{31}P NMR (CDCl$_3$) δ 19.2

Example 19

25   N-methyl pepiridine diethyl phosphonate 21: A solution of compound 20 (22.2 mg, 0.0278 mmol) in THF (1.5 mL) at 0°C was treated with a solution of borane in THF (1M, 0.083 mL). The mixture was stirred for 2 h at room temperature and the starting material was consumed completely as monitored by TLC. The reaction mixture was cooled in an ice/water bath and excess methanol (1 mL) was added to quench the reaction. The solution was concentrated in

30   vacuo and the crude product was chromatographed on silica gel with MeOH/EtOAc to afford compound 21 (7 mg, 32%). ^{1}H NMR (CDCl$_3$) δ 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88

(d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.24 (m, 4H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.62-3.15 (m, 9H), 2.26 (s, 3H), 1.52-2.15 (m, 10H), 1.36 (t, 6H). ^{31}P NMR (CDCl$_3$) δ 19.3

Example Section G

Example 1

Compound 1: To a solution of 4-nitrobenzyl bromide (21.6 g, 100 mmol) in toluene (100

5   mL) was added triethyl phosphite (17.15 mL, 100 mL). The mixture was heated at 120°C for 14 hrs. The evaporation under reduced pressure gave a brown oil, which was purified by flash column chromatography (hexane/EtOAc= 2/1 to 100 % EtOAc) to afford compound 1.

Example 2

10   Compound 2: To a solution of compound 1 (1.0 g) in ethanol (60 mL) was added 10% Pd-C (300 mg). The mixture was hydrogenated for 14 hrs. Celite was added and the mixture was stirred for 5 mins. The mixture was filtered through a pad of celite, and washed with ethanol. Concentration gave compound 2.

Example 3

15   Compound 3: To a solution of compound 3 (292 mg, 1.2 mmol) and aldehyde (111 mg, 0.2 mmol) in methanol (3 mL) was added acetic acid (48 μL, 0.8 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added,

20   and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 3.

Example 4

25   Compound 4: To a solution of compound 3 (79 mg , 0.1 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column

30   chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 4.

Example 5

Compound 5: To a solution of compound 4 (0.1 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (22 mg, 0.18 mmol), followed by bisfurancarbonate (27 mg, 0.09 mmol). The

35   mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed

with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$.

Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford

compound 5 (50 mg): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.11 (2 H, d, J = 8.5 Hz),

6.98 (2 H, d, J = 8.9 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.45 (1 H, m),

5   5.13 (1 H, m), 4.0 (6 H, m), 3.98-3.70 (4 H, m), 3.86 (3 H, s), 3.38 (2 H, m), 3.22 (1 H, m),

3.02 (5 H, m), 2.8 (1 H, m), 2.0-1.8 (3 H, m), 1.26 (6 H, t, J = 7.0 Hz), 0.95 (3 H, d, J = 6.7

Hz), 0.89 (3 H, d, J = 6.7 Hz).

Example 6

10   Compound 6: To a solution of compound 5 (30 mg, 0.04 mmol) in MeOH (0.8 mL) was

added 37% fomaldehyde (30 µL, 0.4 mmol), followed by acetic acid (23 µL, 0.4 mmol). The

mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added.

The reaction mixture was stirred for 14 hrs, and diluted with EtOAc. The organic phase was

washed 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Purification

15   by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 6 (11 mg): ^{1}H

NMR ($CDCl_3$) δ 7.60 (2 H, d, J = 8.9 Hz), 7.17 (2 H, m), 6.95 (2 H, d, J = 8.9 Hz), 6.77 (2 H,

d, J = 8.5 Hz), 5.68 (1 H, d, J = 5.2 Hz), 5.21 (1 H, m), 5.09 (1 H, m), 4.01 (6 H, m), 3.87 (3

H, s), 3.8-3.3 (4 H, m), 3.1-2.6 (7 H, m), 2.90 (3 H, s), 1.8 (3 H, m), 1.25 (6 H, m), 0.91 (6 H,

m).

20

Example 7

Compound 7: To a solution of compound 1 (24.6 g, 89.8 mmol) in acetonitrile (500 mL) was

added TMSBr (36 mL, 269 mmol). The reaction mixture was stirred for 14 hrs, and

evaporated under reduced pressure. The mixture was coevaporated with MeOH (2x), toluene

25   (2x), EtOAc (2x), and CH_2Cl_2 to give a yellow solid (20 g). To the suspension of above

yellow solid (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by

thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at 60°C for 5 hrs, and

evaporated under reduced pressure. The mixture was coevaporated with toluene (2x),

EtOAc, and CH_2Cl_2 (2x) to afford a brown solid. To the solution of the brown solid in

30   CH_2Cl_2 at 0°C was added benzyl alcohol (29 mL, 290 mmol), followed by slow addition of

pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to 25°C and stirred

for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with

EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration

gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) to afford compound 7.

Example 8

5   Compound 8: To a solution of compound 7 (15.3 g) in acetic acid (190 mL) was added Zinc dust (20 g). ·The mixture was stirred for 14 hrs, and celite was added. The suspension was filtered through a pad of celite, and washed with EtOAc. The solution was concentrated under reduced pressure to dryness. The mixture was diluted with EtOAc, and was washed with 2N NaOH (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration under

10   reduced pressure gave compound 8 as an oil (15 g).

Example 9

Compound 9: To a solution of compound 8 (13.5 g, 36.8 mmol) and aldehyde (3.9 g, 7.0 mmol) in methanol (105 mL) was added acetic acid (1.68 mL, 28 mmol). The mixture was

15   stirred for 5 mins, and sodium cyanoborohydride (882 mg, 14 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 9 (6.0 g).

20

Example 10

Compound 10: To a solution of compound 9 (6.2 g , 6.8 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The

25   oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 10.

Example 11

30   Compound 11: To a solution of compound 10 (5.6 mmol) in acetonitrile (60 mL) at 0°C was added DMAP (1.36g, 11.1 mmol), followed by bisfurancarbonate (1.65 g, 5.6 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$.

Purification by flash column chromotography (CH$_2$Cl$_2$/MeOH = 100/3 to 100/5) afford

compound 11 (3.6 g): ^{1}H NMR (CDCl$_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.30 (10 H, m), 7.07 (2

H, m), 6.97 (2 H, d, J = 8.9 Hz), 6.58 (2 H, d, J = 8.2 Hz), 5.70 (1 H, d, J = 5.2 Hz), 5.42 (1

H, m), 5.12 (1 H, m), 4.91 (4 H, m), 4.0-3.7 (6 H, m), 3.85 (3 H, s), 3.4 (2 H, m), 3.25 (1 H,

m), 3.06 (2 H, d, J = 21 Hz), 3.0 (3 H, m), 2.8 (1 H, m), 1.95 (1 H, m), 1.82 (2 H, m), 0.91 (6

H, m).

Example 12

Compound 12: To a solution of compound 11 (3.6 g) in ethanol (175 mL) was added 10%

Pd-C (1.5 g). The reaction mixture was hydrogenated for 14 hrs. The mixture was stirred

with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced

pressure gave compound 12 as a white solid (2.8 g): ^{1}H NMR (DMSO-d$_6$) δ 7.68 (2 H, m),

7.08 (2 H, m), 6.93 (2 H, m), 6.48 (2 H, m), 5.95 (1 H, m), 5.0 (2 H, m), 3.9-3.6 (6 H, m),

3.82 (3 H, s), 3.25 (3 H, m), 3.05 (4 H, m), 2.72 (2 H, d, J = 20.1 Hz), 2.0-1.6 (3 H, m), 0.81

(6 H, m).

Example 13

Compound 13: Compound 12 (2.6 g, 3.9 mmol) and L-alanine ethyl ester hydrochloride

(3.575 g, 23 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in

pyridine (20 mL) and diisopropylethylamine (4.1 mL, 23 mmol) was added. To above

mixture was added a solution of Aldrithiol (3.46 g, 15.6 mmol) and triphenylphosphine (4.08

g, 15.6 g) in pyridine (20 mL). The reaction mixture was stirred for 20 hrs, and solvents were

evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was

washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over MgSO$_4$.

Concentration under reduced pressure gave a yellow oil, which was purified by flash column

chromatography (CH$_2$Cl$_2$/MeOH = 100/5 to100/10) to afford compound 13 (750 mg): ^{1}H

NMR (CDCl$_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.13 (2 H, m), 6.98 (2 H, d, J = 8.8 Hz), 6.61 (2 H,

d, J = 8.0 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.54 (1 H, m), 5.16 (1 H, m), 4.15 (6 H, m), 4.1-3.6

(6 H, m), 3.86 (3 H, s), 3.4-3.2 (3 H, m), 3.1-2.8 (8 H, m), 2.0 (1 H, m), 1.82 (2 H, m), 1.3 (12

H, m), 0.92 (6 H, m).

Example 14

Compound 14: To a solution of 4-hydroxypiperidine (19.5 g, 193 mmol) in THF at 0°C was

added sodium hydroxide solution (160 mL, 8.10 g, 203 mmol), followed by di-tert-butyl

dicarbonate (42.1 g, 193 mmol). The mixture was warmed to 25°C, and stirred for 12 hours.

THF was removed under reduced pressure, and the aqueous phase was extracted with EtOAc

(2x). The combined organic layer was washed with water (2x) and brine, and dried over

5   MgSO4. Concentration gave a compound 14 as a white solid (35 g).

Example 15

Compound 15: To a solution of alcohol 14 (5.25 g, 25 mmol) in THF (100 mL) was added

sodium hydride (1.2 g, 30 mmol, 60%). The suspension was stirred for 30 mins, and

10   chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) was added. Starting material alcohol 14

still existed after 12 hrs. Dimethy sulfoxide (50 mL) and additional chloromethyl methyl

sulfide (2.3 mL, 27.5 mmol) were added. The mixture was stirred for additional 3 hrs, and

THF was removed under reduced pressure. The reaction was quenched with water, and

extracted with ethyl acetate. The organic phase was washed with water and brine, and was

15   dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 8/1)

gave compound 15 (1.24 g).

Example 16

Compound 16: To a solution of compound 15 (693 mg, 2.7 mmol) in CH_2Cl_2 (50 mL) at –

20   78°C was added a solution of sulfuryl chloride (214 µL, 2.7 mmol) in CH_2Cl_2 (5 mL). The

reaction mixture was kept at –78°C for 3 hrs, and solvents were removed to give a white

solid. The white solid was dissolved in toluene (7 mL), and triethyl phosphite (4.5 mL, 26.6

mmol) was added. The reaction mixture was heated at 120°C for 12 hrs. Solvent and excess

reagent was removed under reduced pressure to give compound 16.

25

Example 17

Compound 17: To a solution of compound 17 (600 mg) in CH_2Cl_2 (10 mL) was added

trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under

reduced pressure to give an oil. The oil was diluted with methylene chloride and base resin

30   was added. The suspension was filtered and the organic phase was concentrated to give

compound 17.

Example 18

Compound 18: To a solution of compound 17 (350 mg, 1.4 mmol) and aldehyde (100 mg, 0.2 mmol) in methanol (4 mL) was added acetic acid (156 µL, 2.6 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (164 mg, 2.6 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water

5 was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over MgSO₄. Purification by flash column chromatography (CH₂Cl₂/MeOH = 100/3) gave compound 18 (62 mg).

Example 19

10 Compound 19: To a solution of compound 18 (62 mg, 0.08 mmol) in THF (3 mL) were added acetic acid (9 µL, 0.15 mmol) and tetrabutylamonium fluoride (0.45 mL, 1.0 N, 0.45mmol). The mixture was stirred for 3 hr, and solvent was removed. Purification by flash column chromotogaphy (CH₂Cl₂/MeOH = 100/5) gave an oil. To a solution of above oil in CH₂Cl₂ (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 1 hrs, and

15 was concentrated under reduced pressure. Coevaporation with EtOAc and CH₂Cl₂ gave compound 19.

Example 20

Compound 20: To a solution of compound 19 (55 mg 0.08 mmol) in acetonitrile (1 mL) at

20 0°C was added DMAP (20 mg, 0.16 mmol), followed by bisfurancarbonate (24 mg, 0.08 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over MgSO₄. Purification by flash column chromotography (CH₂Cl₂/MeOH = 100/3 to 100/5) afford compound 20 (46 mg): ¹H NMR (CDCl₃) δ 7.70 (2 H, d, J = 8.9 Hz), 7.01 (2 H, d, J =

25 8.9 Hz), 5.73 (1 H, d, J = 5.1 Hz), 5.51 (1 H, m), 5.14 (1 H, m), 4.16 (1 H, m), 4.06 (1 H, m), 3.94 (3 H, m), 3.86 (3 H, s), 3.80 (1 H, m), 3.75 (2 H, d, J = 9.1 Hz), 3.58 (1 H, m), 3.47 (1 H, m), 3.30 (1 H, m), 3.1-2.6 (8 H, m), 2.3 (2 H, m), 2.1-1.8 (5 H, m), 1.40 (2 H, m), 1.36 (6 H, t, J = 7.0 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.86 (3 h, d, J = 6.7 Hz).

30 Example 21

Compound 21: Compound 21 was made from Boc-4-Nitro-L-Phenylalanine (Fluka) following the procedure for Compound 2 in Scheme Section A, Scheme 1.

Example 22

Compound 22: To a solution of chloroketone 21 (2.76 g, 8 mmol) in THF (50 mL) and water

(6 mL) at 0°C (internal temperature) was added solid NaBH₄ (766 mg, 20 mmol) in several

portions over a period of 15 min while maintaining the internal temperature below 5°C. The

5   mixture was stirred for 1.5 hrs at 0°C and solvent was removed under reduced pressure. The

mixture was quenched with saturated KHSO₃ and extracted with EtOAc. The organic phase

was washed with waster and brine, and dried overMgSO₄. Concentration gave a solid, which

was recrystalized from EtOAc/hexane (1/1) to afford the chloroalcohol 22 (1.72 g).

10   Example 23

Compound 23: To a suspension of chloroalcohol 22 (1.8 g, 5.2 mmol) in EtOH (50 mL) was

added a solution of KOH in ethanol (8.8 mL, 0.71 N, 6.2 mmol). The mixture was stirred for

2 h at room temperature and ethanol was removed under reduced pressure. The reaction

mixture was diluted with EtOAc, and washed with water (2x), saturated NH₄Cl (2x), water,

15   and brine, and dried over MgSO₄. Concentration under reduced pressure afforded epoxide 23

(1.57g) as a white crystalline solid.

Example 24

Compound 24: To a solution of epoxide 23 (20 g, 65 mmol) in 2-propanol (250 mL) was

20   added isobutylamine (65 mL) and the solution was refluxed for 90 min. The reaction mixture

was concentrated under reduced pressure and was coevaporated with MeOH, CH₃CN, and

CH₂Cl₂ to give a white solid. To a solution of the white solid in CH₂Cl₂ (300 mL) at 0°C was

added triethylamine (19 mL, 136 mmol), followed by the addition of 4-

methoxybenzenesulfonyl chloride (14.1 g, 65 mmol) in CH₂Cl₂ (50 mL). The reaction

25   mixture was stirred at 0°C for 30 min, and warmed to room temperature and stirred for

additional 2 hrs. The reaction solution was concentrated under reduced pressure and was

diluted with EtOAc. The organic phase was washed with saturated NaHCO₃, water and

brine, and dried over MgSO₄. Concentration under reduced pressure gave compound 24 as a

white solid (37.5 g).

30

Example 25

Compound 25: To a solution of compound 24 (37.5 g, 68 mmol) in CH₂Cl₂ (100 mL) at 0°C

was added a solution of tribromoborane in CH₂Cl₂ (340 mL, 1.0 N, 340 mmol). The reaction

mixture was kept at 0°C for 1 hr, and warmed to room temperature and stirred for additional

3 hrs. The mixture was cooled to 0°C, and methanol (200 mL) was added slowly. The

mixture was stirred for 1 hr and solvents were removed under reduced pressure to give a

brown oil. The brown oil was coevaporated with EtOAc and toluene to afford compound 25

5   as a brown solid, which was dried under vacuum for 48 hrs.

Example 26

Compound 26: To a solution of compound 25 in THF (80 mL) was added a saturated sodium

bicarbonate solution (25 mL), followed by a solution of Boc2O (982 mg, 4.5 mmol) in THF

10 (20 mL). The reaction mixture was stirred for 5 hrs. THF was removed under reduced

pressure, and aqueous phase was extracted with EtOAc. The organic phase was washed with

water (2x) and Brine (1x), and dried over MgSO$_4$. Purification by flash column

chromatography (hexanes/EtOAc = 1/1) gave compound 26 (467 mg).

15 Example 27

Compound 27: To a solution of compound 26 (300 mg, 0.56 mmol) in THF (6 mL) was

added Cs$_2$CO$_3$ (546 mg, 1.68 mmol), followed by a solution of triflate (420 mg, 1.39 mmol)

in THF (2 mL). The reaction mixture was stirred for 1.5 hrs. The mixture was diluted with

EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO$_4$. Purification by

20 flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 27 (300 mg).

Example 28

Compound 28: To a solution of compound 27 (300 mg, 0.38 mmol) in CH$_2$Cl$_2$ (2 mL) was

added trifluoroacetic acid (2 mL). The mixture was stirred for 2.5 hrs, and was concentrated

25 under reduced pressure. The mixture was diluted with EtOAc and was washed with 0.5 N

NaOH solution (3x), water (2x), and brine (1x), and dried over MgSO$_4$. Concentration gave a

white solid. To the solution of above white solid in acetonitrile (3 mL) at 0°C was added

DMAP (93 mg, 0.76 mmol), followed by bisfurancarbonate (112 mg, 0.38 mmol). The

mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed

30 with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over MgSO$_4$.

Purification by flash column chromotography (CH$_2$Cl$_2$/MeOH = 100/3 to 100/5) afford

compound 28 (230 mg): ^{1}H NMR (CDCl$_3$) δ 8.16 (2 H, d, J = 8.5 Hz), 7.73 (2 H, d, J = 9.2

Hz), 7.42 (2 H, d, J = 8.5 Hz), 7.10 (2 H, d, J = 9.2 Hz), 5.65 (1 H,d, J = 4.8 Hz), 5.0 (2 H,

m), 4.34 (2 H, d, J = 10 Hz), 4.25 (4 H, m), 4.0-3.6 (6 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.6 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.95 (6 H, m).

Example 29

5   Compound 29: To a solution of compound 28 (50 mg) in ethanol (5 mL) was added 10% Pd-C (20 mg). The mixture was hydrogenated for 5 hrs. Celite was added, and the mixture was stirred for 5 mins. The reaction mixture was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (50 mg): ^{1}H NMR (CDCl3) δ 7.72 (2 H, d, J = 8.8 Hz), 7.07 (2 H, 2 H, d, J = 8.8 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.67 (1

10   H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.90 (1 H, m), 4.34 (2 H, d, J = 10.3 Hz), 4.26 (2 H, m), 4.0-3.7 (6 H, m), 3.17 (1 H, m), 2.95 (4 H, m), 2.75 (2 H, m), 1.82 (1 H, m), 1.65 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.93 (3 h, d, J = 6.4 Hz), 0.87 (3 h, d, J = 6.4 Hz).

Example 30

15   Compound 30: To a solution of compound 29 (50 mg, 0.07 mmol) and formaldehyde (52 µL, 37%, 0.7 mmol) in methanol (1 mL) was added acetic acid (40 µL, 0.7 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (44 mg, 0.7 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH

20   solution (1x), water (2x), and brine (1x), and was dried over MgSO4. Purification by flash column chromatography (CH2Cl2/MeOH = 100/3) gave compound 30 (40 mg): ^{1}H NMR (CDCl3) δ 7.73 (2 H, d, J = 8.9 Hz), 7.10 (4 H, m), 6.66 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.02 (1 H, m), 4.88 (1 H, m), 4.32 (2 H, d, J = 10.1 Hz), 4.26 (4 H, m), 3.98 (1 H, m), 3.85 (3 H, m), 3.75 (2 H, m), 3.19 (1 H, m), 2.98 (4 H, m), 2.93 (6 H, s), 2.80 (2 H, m),

25   1.82 (1 H, m), 1.62 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.90 (6 H, m).

Example 31

Compound 31: To a suspension of compound 25 (2.55 g, 5 mmol) in CH2Cl2 (20 mL) at 0°C was added triehtylamine (2.8 mL, 20 mmol), followed by TMSCl (1.26 mL, 10 mmol). The

30   mixture was stirred at 0°C for 30 mins, and warmed to 25°C and stirred for additional 1 hr. Concentration gave a yellow solid. The yellow solid was dissolved in acetonitrile (30 mL) and cooled to 0°C. To this solution was added DMAP (1.22 g, 10 mmol) and Bisfurancarbonate (1.48 g, 5 mmol). The reaction mixture was stirred at 0°C for 2 hrs and for

additional 1 hr at 25°C. Acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with 5% citric acid (2x), water (2x), and brine (1x), and dried over MgSO₄. Concentration gave a yellow solid. The yellow solid was dissolved in THF (40 mL), and acetic acid (1.3 mL, 20 mmol) and tetrabutylammonium fluoride (8mL,

5   1.0 N, 8mmol) were added. The mixture was stirred for 20 mins, and THF was removed under reduced pressure. Purification by flash column chromatography (hexenes/EtOAc = 1/1) gave compound 31 (1.5 g).

Example 32

10   Compound 32: To a solution of compound 31 (3.04 g, 5.1 mmol) in THF (75 mL) was added Cs₂CO₃ (3.31 g, 10.2 mmol), followed by a solution of triflate (3.24 g, 7.65 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs, and THF was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 1/1

15   to 1/3) gave compound 32 (2.4 g): ^{1}H NMR (CDCl₃) δ 8.17 (2 H, d, J = 8.5 Hz), 7.70 (2 H, J = 9.2 Hz), 7.43 (2 H, d, J = 8.5 Hz), 7.37 (10 H, m), 6.99 (2 H, d, J =9.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.15 (4 H, m), 5.05 (2 H, m), 4.26 (2 H, d, J = 10.2 Hz), 3.9-3.8 (4 H, m), 3.75 (2 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 0.92 (6 H, m).

20   Example 33

Compound 33: To a solution of compound 32 (45 mg) in acetic acid (3 mL) was added zinc (200 mg). The mixture was stirred for 5 hrs. Celite was added, and the mixture was filtered and washed with EtOAc. The solution was concentrated to dryness and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution, water, and brine, and dried over

25   MgSO₄. Purification by flash column chromatography (CH₂Cl₂/isoproanol = 100/5) gave compound 33 (25 mg): ^{1}H NMR (CDCl₃) δ 7.67 (2 H, d, J = 8.8 Hz), 7.36 (10 H, m), 6.98 (4 H, m), 6.60 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 4.9 Hz), 5.12 (4 H, m), 5.05 (1 H, m), 4.90 (1 H, m), 4.24 (2 H, d, J = 10.4 Hz), 4.0-3.6 (6 H, m), 3.12 (1 H, m), 3.95 (4 H, m), 2.75 (2 H, m), 1.80 (1 H, m), 1.2 (2 H, m), 0.9 (6 H, m).

30

Example 34

Compound 34: To a solution of compound 32 (2.4 g) in ethanol (140 mL) was added 10% Pd-C (1.0 g). The mixture was hydrogenated for 14 hrs. Celite was added, and the mixture

was stirred for 5 mins. The slurry was filtered through a pad of celite, and washed with pyridine. Concentration under reduced pressure gave compound 34: ^{1}H NMR (DMSO-d$_6$) δ 7.67 (2 H, d, J = 8.9 Hz), 7.14 (2 H, d, J = 8.9 Hz), 6.83 (2 H, d, J = 8.0 Hz), 6.41 (2 H, d, J = 8.0 Hz), 5.51 (1 H, d, J = 5.2 Hz), 5.0-4.8 (2 H, m), 4.15 (2 H, d, J = 10.0 Hz), 3.9-3.2 (8 H, m), 3.0 (2 H, m), 2.8 (4 H, m), 2.25 (1 H, m), 1.4 (2 H, m), 0.8 (6 H, m).

Example 35

Compound 35: Compound 34 (1.62 g, 2.47 mmol) and L-alanine butyl ester hydrochloride (2.69 g, 14.8 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (12 mL) and diisopropylethylamine (2.6 mL, 14.8 mmol) was added. To above mixture was added a solution of Aldrithiol (3.29 g, 14.8 mmol) and triphenylphosphine (3.88 g, 14.8 g) in pyridine (12 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over MgSO$_4$. Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH = 100/5 to100/15) to afford compound 35 (1.17 g): ^{1}H NMR (CDCl$_3$) δ 7.70 (2 H, d, J = 8.6 Hz), 7.05 (2 H, d, J =8.6 Hz), 6.99 (2 H, d, J = 8.0 Hz), 6.61 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.96 (1 H, m), 4.28 (2 H, m), 4.10 (6 H, m), 4.0-3.6 (6 H, m), 3.12 (2 H, m), 2.92 (3 H, m), 2.72 (2 H, m), 1.82 (1 H, m), 1.75-1.65 (2 H, m), 1.60 (4 H, m), 1.43 (6 H, m), 1.35 (4 H, m), 0.91 (12 H, m).

Example 36

Compound 37: Compound 36 (100 mg, 0.15 mmol) and L-alanine butyl ester hydrochloride (109 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over MgSO$_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH = 100/5 to100/15) to afford compound 37 (21 mg): ^{1}H NMR (CDCl$_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.2 Hz), 7.01 (2 H, d, J = 8.8 Hz), 6.87 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.03 (1 H, m), 4.95 (1 H, m), 4.2-4.0 (8 H, m), 3.98 (1 H, m), 3.89 (3 H, s),

3.88-3.65 (5 H, m), 3.15 (1 H, m), 2.98 (4 H, m), 2.82 (2 H, m), 1.83 (1 H, m), 1.63 (4 H, m), 1.42 (6 H, m), 1.35 (4 H, m), 0.95 (12 H, m).

Example 37

5   Compound 38: Compound 36 (100 mg, 0.15 mmol) and L-leucine ethyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents

10   were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 38 (12 mg): ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.5 Hz), 7.14 (2 H, d, J = 8.0 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.86 (2 H, d, J = 8.0 Hz), 5.66 (1 H,

15   d, J = 5.2 Hz), 5.05 (1 H, m), 4.95 (1 H, m), 4.2-4.0 (8 H, m), 4.0-3.68 (6 H, m), 3.88 (3 H, s), 3.2-2.9 (5 H, m), 2.80 (2 H, m), 1.80 (1 H, m), 1.65 (4 H, m), 1.65-1.50 (4 H, m), 1.24 (6 H, m), 0.94 (18 H, m).

Example 38

20   Compound 39: Compound 36 (100 mg, 0.15 mmol) and L-leucine butyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents

25   were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 39 (32 mg): ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.0 Hz), 7.0 (2 H, d, J = 8.8 Hz), 6.89 (2 H, d, J = 8.0 Hz), 5.66 (1 H, d,

30   J = 4.3 Hz), 5.07 (1 H, m), 4.94 (1 H, m), 4.2-4.0 (8 H, m), 3.89 (3 H, s), 4.0-3.6 (6 H, m), 3.2-2.9 (5 H, m), 2.8 (2 H, m), 1.81 (1 H, m), 1.78-1.44 (10 H, m), 1.35 (4 H, m), 0.95 (24 H, m).

Example 39

Compound 41: Compound 40 (82 mg, 0.1 mmol) and L-alanine isopropyl ester

hydrochloride (92 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was

dissolved in pyridine (1 mL) and diisopropylethylamine (136 µL, 0.78 mmol) was added. To

5   above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine

(87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs,

and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl

acetate, and was washed with water (2x), and brine, and dried over MgSO$_4$. Concentration

under reduced pressure gave an oil, which was purified by flash column chromatography

10   (CH$_2$Cl$_2$/MeOH = 100/1 to100/3) to afford compound 41 (19 mg): ^{1}H NMR (CDCl$_3$) δ 7.71

(2 H, d, J = 8.9 Hz), 7.2-7.35 (5 H, m), 7.15 (2 H, m), 7.01 (2 H, d, J = 8.9 Hz), 6.87 (2 H, m),

5.65 (1 H, d, J = 5.4 Hz), 5.05-4.93 (2 H, m), 4.3 (2 H, m), 4.19 (1 H, m), 3.98 (1 H, m), 3.88

(3 H, s), 3.80 (2 H, m), 3.70 (3 H, m), 3.18 (1 H, m), 2.95 (4 H, m), 2.78 (2 H, m), 1.82 (1 H,

m), 1.62 (2 H, m), 1.35 (3 H, m), 1.25-1.17 (6 H, m), 0.93 (3 H, d, J = 6.4 Hz), 0.88 (3 H, d, J

15   = 6.4 Hz).

Example 40

Compound 42: Compound 40 (100 mg, 0.13 mmol) and L-glycine butyl ester hydrochloride

(88 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in

20   pyridine (1 mL) and diisopropylethylamine (136 µL, 0.78 mmol) was added. To above

mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87

mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and

solvents were evaporated under reduced pressure. The mixture was diluted with ethyl

acetate, and was washed with water (2x), and brine, and dried over MgSO$_4$. Concentration

25   under reduced pressure gave an oil, which was purified by flash column chromatography

(CH$_2$Cl$_2$/MeOH = 100/1 to100/3) to afford compound 42 (18 mg): ^{1}H NMR (CDCl$_3$) δ 7.71

(2 H, d, J = 9.2 Hz), 7.35-7.24 (5 H, m), 7.14 (2 H, m), 7.00 (2 H, d, J = 8.8 Hz), 6.87 (2 H,

m), 5.65 (1 H, d, J = 5.2 Hz), 5.04 (1 H, m), 4.92 (1 H, m), 4.36 (2 H, m), 4.08 (2 H, m), 3.95

(3 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.76 (3 H, m), 3.54 (1 H, m), 3.15 (1 H, m), 2.97 (4 H,

30   m), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (4 H, m), 1.35 (2 H, m), 0.9 (9 H, m).

Example Section H

Example 1

Sulfonamide 1: To a suspension of epoxide (20 g, 54.13 mmol) in 2-propanol (250 mL) was
added isobutylamine (54 mL, 541 mmol) and the solution was refluxed for 30 min. The
solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2
(250 mL) and cooled to 0°C. Triethylamine (15.1 mL, 108.26 mmol) was added followed by
the addition of 4-nitrobenzenesulfonyl chloride (12 g, 54.13 mmol) and the solution was
stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced
pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic
phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under
reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the
sulfonamide (30.59 g, 90%) as an off-white solid.

Example 2

Phenol 2: A solution of sulfonamide 1 (15.58 g, 24.82 mmol) in EtOH (450 mL) and CH_2Cl_2
(60 mL) was treated with 10% Pd/C (6 g). The suspension was stirred under H_2 atmosphere
(balloon) at room temperature for 24 h. The reaction mixture was filtered through a plug of
celite and concentrated under reduced pressure. The crude product was purified by column
chromatography on silica gel (6% $MeOH/CH_2Cl_2$) to give the phenol (11.34 g, 90%) as a
white solid.

Example 3

Dibenzylphosphonate 3: To a solution of phenol 2 (18.25 g, 35.95 mmol) in CH_3CN (200
mL) was added Cs_2CO_3 (23.43 g, 71.90 mmol) and triflate (19.83 g, 46.74 mmol). The
reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated
under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl.
The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure.
The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane)
to give the dibenzylphosphonate (16.87 g, 60%) as a white solid.

Example 4

Amine 4: A solution of dibenzylphosphonate (16.87 g, 21.56 mmol) in CH_2Cl_2 (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH.

5   The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (12.94 g, 88%) as a white solid.

Example 5

10   Carbonate 5: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (5.00 g, 56.75 mmol) in CH_2Cl_2 (80 mL) was added triethylamine (11.86 mL, 85.12 mmol) and bis(4-nitrophenyl)carbonate (25.90 g, 85.12 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The CH_2Cl_2 layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by

15   column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (8.62 g, 60%) as a pale yellow oil which solidified upon refrigerating.

Example 6

Carbamate 6: Two methods have been used.

20   Method 1: To a solution of 4 (6.8 g, 9.97 mmol) and 5 (2.65 g, 10.47 mmol) in CH_3CN (70 mL) at 0 °C was added 4-(dimethylamino)pyridine (2.44 g, 19.95 mmol). The reaction mixture was stirred at 0°C for 3 h and concentrated. The residue was dissolved in EtOAc and washed with 0.5 N NaOH, saturated $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3%

25   2-propanol/CH_2Cl_2) to give the carbamate (3.97 g, 50%) as a pale yellow solid.

Method 2: To a solution of 4 (6.0 g, 8.80 mmol) and 5 (2.34 g, 9.24 mmol) in CH_3CN (60 mL) at 0°C was added 4-(dimethylamino)pyridine (0.22 g, 1.76 mmol) and N, N-diisopropylethylamine (3.07 mL, 17.60 mmol). The reaction mixture was stirred at 0°C for 1

30   h and warmed to room temperature overnight. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with 0.5 N NaOH, saturated $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product

was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the carbamate (3.85 g, 55%) as a pale yellow solid.

Example 7

5   Phosphonic Acid 7: To a solution of 6 (7.52 g, 9.45 mmol) in MeOH (350 mL) was added 10% Pd/C (3 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 48 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (5.24 g, 90%) as a white solid.

10

Example 8

Cbz Amide 8: To a solution of 7 (5.23 g, 8.50 mmol) in CH$_3$CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (16.54 mL, 68 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-

15   evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH$_2$Cl$_2$ (40 mL) at 0°C was added pyridine (1.72 mL, 21.25 mmol) and benzyl chloroformate (1.33 mL, 9.35 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl

20   (150 mL) was added at 0°C and stirred for 30 min. CH$_2$Cl$_2$ was added and two layers were separated. The organic layer was dried with Na$_2$SO$_4$, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.46 g, 70%) as an off-white solid.

25   Example 9

Diphenylphosphonate 9: A solution of 8 (4.454 g, 5.94 mmol) and phenol (5.591 g, 59.4 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.903 g, 23.76 mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off.

30   The filtrate was concentrated and dissolved in CH$_3$CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by

column chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the
diphenylphosphonate (2.947 g, 55%) as a white solid.

Example 10

5   Monophosphonic Acid 10: To a solution of 9 (2.945 g, 3.27 mmol) in CH$_3$CN (25 mL) at
0°C was added 1N NaOH (8.2 mL, 8.2 mmol). The reaction mixture was stirred at 0°C for 1
h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred
for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-
evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give
10 the monophosphonic acid (2.427 g, 90%) as a white solid.

Example 11

Cbz Protected Monophosphoamidate 11: A solution of 10 (2.421 g, 2.93 mmol) and L-
alanine isopropyl ester hydrochloride (1.969 g, 11.73 mmol) in pyridine (20 mL) was heated
15 to 70°C and 1,3-dicyclohexylcarbodiimide (3.629 g, 17.58 mmol) was added. The reaction
mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was
evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.2 N
HCl. The EtOAc layer was washed with 0.2 N HCl, H$_2$O, saturated NaHCO$_3$, dried with
Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column
20 chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the monoamidate (1.569 g,
57%) as a white solid.

Example 12

Monophosphoamidate 12: To a solution of 11 (1.569 g, 1.67 mmol) in EtOAc (80 mL) was
25 added 10% Pd/C (0.47 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room
temperature overnight. The reaction mixture was filtered through a plug of celite. The
filtrate was concentrated and the crude product was purified by column chromatography on
silica gel (CH$_2$Cl$_2$ to 1-8% 2-propanol/CH$_2$Cl$_2$) to give the monophosphoamidate 12a (1.12 g,
83%, GS 108577, 1:1 diastereomeric mixture A/B) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.45
30 (dd, 2H), 7.41-7.17 (m, 7H), 6.88 (dd, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.95
(m, 1H), 4.37-4.22 (m, 5H), 3.82-3.67 (m, 7H), 2.99-2.70 (m, 6H), 2.11-1.69 (m, 3H), 1.38
(m, 3H), 1.19 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ
20.5, 19.6. 12b (29 mg, 2%, GS108578, diastereomer A) as a white solid: ^{1}H NMR (CDCl$_3$)

δ 7.43 (d, J = 7.8 Hz, 2H), 7.35-7.17 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.96 (m, 1H), 4.38-4.32 (m, 4H), 4.20 (m, 1H), 3.82-3.69 (m, 7H), 2.99-2.61 (m, 6H), 2.10 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 6.3 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ

5   20.5. 12c (22 mg, 1.6%, **GS 108579**, diastereomer B) as a white solid : ^{1}H NMR (CDCl$_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.36-7.20 (m, 7H), 6.87 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.15 (broad s, 1H), 4.95 (m, 1H), 4.34-4.22 (m, 5H), 3.83-3.67 (m, 7H), 2.99-2.64 (m, 6H), 2.11-1.68 (m, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.0 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 19.6.

10

Example 13

Sulfonamide 13: To a suspension of epoxide (1.67 g, 4.52 mmol) in 2-propanol (25 mL) was added isobutylamine (4.5 mL, 45.2 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$

15   (20 mL) and cooled to 0°C. Triethylamine (1.26 mL, 9.04 mmol) was added followed by the treatment of 3-nitrobenzenesulfonyl chloride (1.00 g, 4.52 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under

20   reduced pressure. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the sulfonamide (1.99 g, 70%) as a white solid.

Example 14

Phenol 14: Sulfonamide 13 (1.50 g, 2.39 mmol) was suspended in HOAc (40 mL) and
25   concentrated HCl (20 mL) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was partitioned between 10% MeOH/CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layers were washed with NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated to give a yellow solid. The crude product was dissolved in CHCl$_3$ (20 mL) and treated with triethylamine (0.9

30   mL, 6.45 mmol) followed by the addition of Boc$_2$O (0.61 g, 2.79 mmol). The reaction mixture was stirred at room temperature for 6 h. The product was partitioned between CHCl$_3$ and H$_2$O. The CHCl$_3$ layer was washed with NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-5%

MeOH/CH$_2$Cl$_2$) to give the phenol (0.52 g, 45%) as a pale yellow solid.

Example 15

Dibenzylphosphonate 15: To a solution of phenol 14 (0.51 g, 0.95 mmol) in CH$_3$CN (8 mL)

5   was added Cs$_2$CO$_3$ (0.77 g, 2.37 mmol) and triflate (0.8 g, 1.90 mmol). The reaction mixture

was stirred at room temperature for 1.5 h and the solvent was evaporated under reduced

pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic

phase was dried Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product

was purified by column chromatography on silica gel (3% MeOH/CH$_2$Cl$_2$) to give the

10   dibenzylphosphonate (0.62 g, 80%) as a white solid.

Example 16

Amine 16: A solution of dibenzylphosphonate 15 (0.61 g, 0.75 mmol) in CH$_2$Cl$_2$ (8 mL) at

0°C was treated with trifluoroacetic acid (2 mL). The solution was stirred for 30 min at 0°C

15   and then warmed to room temperature for an additional 30 min. Volatiles were evaporated

under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH.

The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried

(Na$_2$SO$_4$), filtered, and evaporated under reduced pressure to give the amine (0.48 g, 90%)

which was used directly without any further purification.

20

Example 17

Carbamate 17: To a solution of amine 16 (0.48 g, 0.67 mmol) in CH$_3$CN (8 mL) at 0°C was

treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (0.2 g,

0.67 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and 4-

25   (dimethylamino)pyridine (0.17 g, 1.34 mmol). After stirring for 2 h at 0°C, the reaction

solvent was evaporated under reduced pressure and the residue was partitioned between

EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric

acid (2 x), saturated NaHCO$_3$, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced

pressure. The crude product was purified by column chromatography on silica gel (3% 2-

30   propanol/CH$_2$Cl$_2$) to give the carbamate (0.234 g, 40%) as a white solid.

Example 18

Analine 18: To a solution of carbamate 17 (78 mg, 0.09 mmol) in 2 mL HOAc was added

zinc powder. The reaction mixture was stirred at room temperature for 1.5 h and filtered

through a small plug of celite. The filtrate was concentrated and co-evaporated with toluene.

The crude product was purified by column chromatography on silica gel (5% 2-

5   propanaol/CH$_2$Cl$_2$) to give the analine (50 mg, 66%) as a white solid.

Example 19

Phosphonic Acid 19: To a solution of analine (28 mg, 0.033mmol) in MeOH (1 mL) and

HOAc (0.5 mL) was added 10% Pd/C (14 mg). The suspension was stirred under H$_2$

10   atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through

a small plug of celite. The filtrate was concentrated, co-evaporated with toluene, and dried

under vacuum to give the phosphonic acid (15 mg, 68%, GS 17424) as a white solid: ^{1}H

NMR (DMSO-d$_6$) δ 7.16-6.82 (m, 8H), 5.50 (d, 1H), 4.84 (m, 1H), 3.86-3.37 (m, 9H), 2.95-

2.40 (m, 6H), 1.98 (m, 1H), 1.42-1.23 (m, 2H), 0.84 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.3

15   Hz,3H). MS (ESI) 657 (M-H).

Example 20

Phenol 21: A suspension of aminohydrobromide salt 20 (22.75 g, 44 mmol) in CH$_2$Cl$_2$ (200

mL) at 0°C was treated with triethylamine (24.6 mL, 176 mmol) followed by slow addition of

20   chlorotrimethylsilane (11.1 mL, 88 mmol). The reaction mixture was stirred at 0°C for 30

min and warmed to room temperature for 1 h. The solvent was removed under reduced

pressure to give a yellow solid. The crude product was dissolved in CH$_2$Cl$_2$ (300 mL) and

treated with triethylamine (18.4 mL, 132 mmol) and Boc$_2$O (12 g, 55 mmol). The reaction

mixture was stirred at room temperature overnight. The product was partitioned between

25   CH$_2$Cl$_2$ and H$_2$O. The CH$_2$Cl$_2$ layer was washed with NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$,

filtered, and concentrated. The crude product was dissolved in THF (200 mL) and treated

with 1.0 M TBAF (102 mL, 102 mmol) and HOAc (13 mL). The reaction mixture was

stirred at room temperature for 1 h and concentrated under reduced pressure. The residue

was partitioned between CH$_2$Cl$_2$ and H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated.

30   The crude product was purified by column chromatography on silica gel (1-3% 2-

propanol/CH$_2$Cl$_2$) to give the phenol (13.75 g, 58%) as a white solid.

Example 21

Dibenzylphosphonate 22: To a solution of phenol 21 (13.70 g, 25.48 mmol) in THF (200 mL) was added Cs$_2$CO$_3$ (16.61 g, 56.96 mmol) and triflate (16.22 g, 38.22 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl.

5   The organic phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH$_2$Cl$_2$) to give the dibenzylphosphonate (17.59 g, 85%) as a white solid.

Example 22

10   Amine 23: A solution of dibenzylphosphonate 22 (17.58 g, 21.65 mmol) in CH$_2$Cl$_2$ (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with

15   Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give the amine (14.64 g, 95%) which was used directly without any further purification.

Example 23

Carbamate 24: To a solution of amine 23 (14.64 g, 20.57 mmol) in CH$_3$CN (200 mL) at 0°C

20   was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (6.07 g, 20.57 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (5.03 g, 41.14mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric

25   acid (2 x), saturated NaHCO$_3$, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the carbamate (10 g, 56%) as a white solid.

Example 24

30   Phosphonic Acid 25: To a solution of carbamate 24 (8 g, 9.22 mmol) in EtOH (500 mL was added 10% Pd/C (4 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 30 h. The reaction mixture was filtered through a plug of celite. The celite paste was suspended in pyridine and stirred for 30 min and filtered. This process was

repeated twice. The combined solution was concentrated under reduced pressure to give the phosphonic acid (5.46 g, 90%) as an off-white solid.

Example 25

5   Cbz Amide 26: To a solution of 25 (5.26 g, 7.99 mmol) in CH3CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (15.6 mL, 63.92 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate

10   in CH2Cl2 (40 mL) at 0°C was added pyridine (1.49 mL, 18.38 mmol) and benzyl chloroformate (1.25mL, 8.79 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH2Cl2 was added and two layers were separated. The organic layer was dried with Na2SO4, filtered, concentrated, co-evaporated

15   with toluene, and dried under vacuum to give the Cbz amide (4.43 g, 70%) as an off-white solid.

Example 26

Diphenylphosphonate 27: A solution of 26 (4.43 g, 5.59 mmol) and phenol (4.21 g, 44.72

20   mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.62 g, 22.36 mmol) was added. The reaction mixture was stirred at 70°C for 36 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The

25   resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane to EtOAc) to give the diphenylphosphonate (2.11 g, 40%) as a pale yellow solid.

Example 27

30   Monophosphonic Acid 28: To a solution of 27 (2.11 g, 2.24 mmol) in CH3CN (15 mL) at 0°C was added 1N NaOH (5.59 mL, 5.59 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-

evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (1.75 g, 90%) as a white solid.

Example 28

5   Cbz Protected Monophosphoamidate 29: A solution of 28 (1.54 g, 1.77 mmol) and L-alanine isopropyl ester hydrochloride (2.38 g, 14.16 mmol) in pyridine (15 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.20 g, 10.62 mmol) was added. The reaction mixture was stirred at 70°C overnight and cooled to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The

10 . EtOAc layer was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the monophosphoamidate (0.70g, 40%) as an off-white solid.

15 ### Example 29

Monophosphoamidate 30a-b: To a solution of 29 (0.70 g, 0.71 mmol) in EtOH (10 mL) was added 10% Pd/C (0.3 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated and the crude products were purified by column chromatography on

20 silica gel (7-10% MeOH/CH_2Cl_2) to give the monoamidates 30a (0.106 g, 18%, GS 77369, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.73-7.16 (m, 5H), 7.10-6.98 9m, 4H), 6.61 (d, J = 8.1 Hz, 2H), 5.67 (d, J = 4.8 Hz, 1H), 5.31-4.91 (m, 2H), 4.44 (m, 2H), 4.20 (m, 1H), 4.00-3.61 (m, 6H), 3.18-2.74 (m, 7H), 1.86-1.64 (m, 3H), 1.38 (m, 3H), 1.20 (m, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);

25 ^{31}P NMR ($CDCl_3$) □ 19.1, 18; MS(ESI) 869 (M+Na). 30b (0.200 g, 33%, GS 77425, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, J = 8.7 Hz, J = 1.5 Hz, 2H), 7.36-7.16 (m, 5H), 7.09-7.00 (m, 4H), 6.53 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.4 Hz, 1H), 5.06-4.91 (m, 2H), 4.40 (m, 2H), 4.20 (m, 1H), 4.00-3.60 (m, 6H), 3.14 (m, 3H), 3.00-2.65 (m, 6H), 1.86-1.60 (m, 3H), 1.35 (m, 3H), 1.20 (m, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.87

30 (d, J = 6.6 Hz, 3H); ^{31} P NMR ($CDCl_3$) □ 19.0, 17.9. MS (ESI) 897 (M+Na).

Example 30

Synthesis of Bisamidates 32: A solution of phosphonic acid 31 (100 mg, 0.15 mmol) and L-valine ethyl ester hydrochloride (108 mg, 0.60 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in

5 pyridine (1 mL) followed by addition of N,N-diisopropylethylamine (0.1 mL, 0.60 mmol). The reaction mixture was stirred at room temperature for two days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the bisamidate (73 mg, 53%, GS 17389) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86 (d,

10 J = 8.1 Hz, 2H), 5.66 (d, J = 4.8 Hz, 1H), 5.05 (m, 1H), 4.95 (d, J = 8.7 Hz, 1H), 4.23-4.00 (m ,4H,), 3.97-3.68 (m, 11H), 3.39-2.77 (m, 9H), 2.16 (m, 2H), 1.82-1.60 (m, 3H), 1.31-1.18 (m, 6H), 1.01-0.87 (m, 18H); ^{31}P NMR (CDCl$_3$) δ 21.3; MS (ESI) 950 (M+Na).

Example 31

15 Triflate 34: To a solution of phenol 33 (2.00 g, 3.46 mmol) in THF (15 mL) and CH$_2$Cl$_2$ (5 mL) was added N-phenyltrifluoromethanesulfonimide (1.40 g, 3.92 mmol) and cesium carbonate (1.40 g, 3.92 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The crude product was partitioned between CH$_2$Cl$_2$ and saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was

20 purified by column chromatography on silica gel (3% MeOH/CH$_2$Cl$_2$) to give the triflate (2.09 g, 85%) as a white solid.

Example 32

Aldehyde 35: To a suspension of triflate 34 (1.45 g, 2.05 mmol), palladium (II) acetate (46

25 mg, 0.20 mmol) and 1,3-bis(diphenylphosphino)propane (84 mg, 0.2 mmol) in DMF (8 mL) under CO atmosphere (balloon) was slowly added triethylamine (1.65 mL, 11.87 mmol) and triethylsilane (1.90 mL, 11.87 mmol). The reaction mixture was heated to 70°C under CO atmosphere (balloon) and stirred overnight. The solvent was concentrated under reduced pressure and partitioned between CH$_2$Cl$_2$ and H$_2$O. The organic phase was dried with

30 Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the aldehyde (0.80 g, 66%) as a white solid.

Example 33

Substituted Benzyl Alcohol 36: To a solution of aldehyde 35 (0.80g, 1.35 mmol) in THF (9
mL) and H$_2$O (1 mL) at –10°C was added NaBH$_4$ (0.13 g, 3.39 mmol). The reaction mixture
was stirred for 1 h at –10°C and the solvent was evaporated under reduced pressure. The
5   residue was dissolved in CH$_2$Cl$_2$ and washed with NaHSO$_4$, H$_2$O, dried with Na$_2$SO$_4$, filtered,
and concentrated. The crude product was purified by column chromatography on silica gel
(6% 2-propanol/CH$_2$Cl$_2$) to give the alcohol (0.56 g, 70%) as a white solid.

Example 34

10   Substituted Benzyl Bromide 37: To a solution of alcohol 36 (77 mg, 0.13 mmol) in THF (1
mL) and CH$_2$Cl$_2$ (1 mL) at 0°C was added triethylamine (0.027 mL, 0.20 mmol) and
methanesulfonyl chloride (0.011 mL, 0.14 mmol). The reaction mixture was stirred at 0°C
for 30 min and warmed to room temperature for 3 h. Lithium bromide (60 mg, 0.69 mmol)
was added and stirred for 45 min. The reaction mixture was concentrated and the residue was
15   partitioned between CH$_2$Cl$_2$ and H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated. The
crude product was purified by column chromatography on silica gel (2% MeOH/CH$_2$Cl$_2$) to
give the bromide (60 mg, 70%).

Example 35

20   Diethylphosphonate 38: A solution of bromide 37 (49 mg, 0.075 mmol) and
triethylphosphite (0.13 mL, 0.75 mmol) in toluene (1.5 mL) was heated to 120°C and stirred
overnight. The reaction mixture was cooled to room temperature and concentrated under
reduced pressure. The crude product was purified by column chromatography on silica gel
(6% MeOH/CH$_2$Cl$_2$) to give the diethylphosphonate (35 mg, 66%, GS 191338) as a white
25   solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.27-7.16 (m, 4H), 7.00 (d, J = 8.7 Hz,
2H), 5.66 (d, J = 5.1 Hz, 1H), 5.00 (m, 2H), 4.04-3.73 (m, 13H), 3.13-2.80 (m, 9H), 1.82-1.64
(m, 3H), 1.25 (t, J = 6.9 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR
(CDCl$_3$) ☐ 26.4; MS (ESI) 735 (M+Na).

30   Example 36

N-tert-Butoxycarbonyl-O-benzyl-L-serine 39: To a solution of Boc-L-serine (15 g, 73.09
mmol) in DMF (300 mL) at 0°C was added NaH (6.43 g, 160.80 mmol, 60% in mineral oil)
and stirred for 1.5 h at 0°C. After the addition of benzyl bromide (13.75 g, 80.40 mmol), the

reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in H$_2$O. The crude product was partitioned between H$_2$O and Et$_2$O. The aqueous phase was acidified to pH<4 with 3 N HCl and extracted with EtOAc three times. The combined EtOAc solution was washed with

5   H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated to give the N-tert-butoxycarbonyl-O-benzyl-L-serine (17.27 g, 80%).

Example 37

Diazo Ketone 40: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-serine 39 (10 g, 33.86

10   mmol) in dry THF (120 mL) at −15°C was added 4-methylmorpholine (3.8 mL, 34.54 mmol) followed by the slow addition of isobutylchloroformate (4.40 mL, 33.86 mmol). The reaction mixture was stirred for 30 min and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an ice bath at

15   0°C and stirred for 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated NaHCO$_3$, saturated NaCl, dried with Na$_2$SO$_4$, filtered and evaporated. The crude product was purified by column chromatography (EtOAc/hexane) to afford the diazo ketone (7.50 g, 69%) as a yellow oil.

20

Example 38

Chloroketone 41: To a suspension of diazoketone 40 (7.50 g, 23.48 mmol) in ether (160 mL) at 0°C was added 4N HCl in dioxane (5.87 mL, 23.48 mmol). The reaction mixture was stirred at 0°C for 1 h. The reaction solvent was evaporated under reduced pressure to give the

25   chloroketone which was used directly without any further purification.

Example 39

Chloroalcohol 42: To a solution of chloroketone 41 (7.70 g, 23.48 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 0°C. A solution of NaBH$_4$ (2.67 g,

30   70.45 mmol) in water (4 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1 h at 0°C and saturated KHSO$_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column

chromatography on silica gel (1/4 EtOAc/hexane) to give the chloroalcohol (6.20 g, 80%) as
a diastereomeric mixture.

Example 40

5   Epoxide 43: A solution of chloroalcohol 42 (6.20 g, 18.79 mmol) in EtOH (150 mL) was
treated with 0.71 M KOH (1.27 g, 22.55 mmol) and the mixture was stirred at room
temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the
residue was partitioned between EtOAc and water. The organic phase was washed with
saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The
10   crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to
afford the desired epoxide 43 (2.79 g, 45%) and a mixture of diastereomers 44 (1.43 g, 23%).

Example 41

Sulfonamide 45: To a suspension of epoxide 43 (2.79 g, 8.46 mmol) in 2-propanol (30 mL)
15   was added isobutylamine (8.40 mL, 84.60 mmol) and the solution was refluxed for 1 h. The
solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$
(40 mL) and cooled to 0°C. Triethylamine (2.36 mL, 16.92 mmol) was added followed by
the addition of 4-methoxybenzenesulfonyl chloride (1.75 g, 8.46 mmol). The solution was
stirred for 40 min at 0°C, warmed to room temperature, and evaporated under reduced
20   pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic
phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under
reduced pressure. The crude product was directly used without any further purification.

Example 42

25   Silyl Ether 46: A solution of sulfonamide 45 (5.10 g, 8.46 mmol) in CH$_2$Cl$_2$ (50 mL) was
treated with triethylamine (4.7 mL, 33.82 mmol) and TMSOTf (3.88 mL, 16.91 mmol). The
reaction mixture was stirred at room temperature for 1 h and partitioned between CH$_2$Cl$_2$ and
saturated NaHCO$_3$. The aqueous phase was extracted twice with CH$_2$Cl$_2$ and the combined
organic extracts were washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and
30   evaporated under reduced pressure. The crude product was purified by column
chromatography on silica gel (1/6 EtOAc/hexane) to give the silyl ether (4.50 g, 84%) as a
thick oil.

<u>Example 43</u>

Alcohol 47: To a solution of silyl ether 46 (4.5 g, 7.14 mmol) in MeOH (50 mL) was added
10% Pd/C (0.5 g). The suspension was stirred under H_2 atmosphere (balloon) at room
temperature for 2 h. The reaction mixture was filtered through a plug of celite and

5   concentrated under reduced pressure. The crude product was purified by column
chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the alcohol (3.40 g, 85%) as a
white solid.

<u>Example 44</u>

10   Aldehyde 48: To a solution of alcohol 47 (0.60 g, 1.07 mmol) in CH_2Cl_2 (6 mL) at 0°C was
added Dess Martin reagent (0.77 g, 1.82 mmol). The reaction mixture was stirred at 0°C for
3 h and partitioned between CH_2Cl_2 and $NaHCO_3$. The organic phase was washed with H_2O,
dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column
chromatography on silica gel (1/4 EtOAc/hexane) to give the aldehyde (0.45 g, 75%) as a

15   pale yellow solid.

<u>Example 45</u>

Sulfonamide 50: To a suspension of epoxide (2.00 g, 5.41 mmol) in 2-propanol (20 mL) was
added amine 49 (4.03 g, 16.23 mmol) (prepared in 3 steps starting from 4-

20   (aminomethyl)piperidine according to Bioorg. Med. Chem. Lett., 2001, 11, 1261.). The
reaction mixture was heated to 80°C and stirred for 1 h. The solution was evaporated under
reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C.
Triethylamine (4.53 mL, 32.46 mmol) was added followed by the addition of 4-
methoxybenzenesulfonyl chloride (3.36 g, 16.23 mmol). The solution was stirred for 40 min

25   at 0°C, warmed to room temperature for 1.5 h, and evaporated under reduced pressure. The
residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was
washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced
pressure. The crude product was purified by column chromatography on silica gel (3% 2-
propanol/CH_2Cl_2) to give the sulfonamide (2.50 g, 59%).

30

<u>Example 46</u>

Amine 51: A solution of sulfonamide 50 (2.50 g, 3.17 mmol) in CH_2Cl_2 (6 mL) at 0°C was
treated with trifluoroacetic acid (3 mL). The solution was stirred for 30 min at 0°C and then

warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried with Na₂SO₄, filtered, and evaporated under reduced pressure to give the amine (1.96 g, 90%)

5   which was used directly without any further purification.

Example 47

Carbamate 52: To a solution of amine 51 (1.96 g, 2.85 mmol) in CH₃CN (15mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (0.84g,

10   2.85mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (0.70 g, 5.70 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated NaHCO₃, dried with Na₂SO₄, filtered, and evaporated under reduced

15   pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the carbamate (1.44 g, 60%) as a white solid.

Example Section I

Example 1

Carbonate 2: To a solution of (R)-(+)-3-hydroxytetrahydrofuran (1.23 g, 14 mmol) in
CH$_2$Cl$_2$ (50 mL) was added triethylamine (2.9 mL, 21 mmol) and bis(4-nitrophenyl)carbonate
(4.7 g, 15.4 mmol). The reaction mixture was stirred at room temperature for 24 h and
partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The CH$_2$Cl$_2$ layer was dried with
Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column
chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (2.3 g, 65%) as a pale
yellow oil which solidified upon standing.

Example 2

Carbamate 3: To a solution of 1 (0.385 g, 0.75 mmol) and 2 (0.210 g, 0.83 mmol) in CH$_3$CN
(7 mL) at room temperature was added N, N-diisopropylethylamine (0.16 mL, 0.90 mmol).
The reaction mixture was stirred at room temperature for 44 h. The solvent was evaporated
under reduced pressure. The crude product was dissolved in EtOAc and washed with
saturated NaHCO$_3$, brine, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product
was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the
carbamate (0.322 g, 69%) as a white solid: mp 98-100°C (uncorrected).

Example 3

Phenol 4: To a solution of 3 (0.31 g, 0.49 mmol) in EtOH (10 mL) and EtOAc (5 mL) was
added 10% Pd/C (30 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at
room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The
filtrate was concentrated and dried under vacuum to give the phenol (0.265 g) in quantitative
yield.

Example 4

Diethylphosphonate 5: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was
added Cs$_2$CO$_3$ (124 mg, 0.38 mmol) and triflate (85 mg, 0.29 mmol). The reaction mixture
was stirred at room temperature for 4 h and the solvent was evaporated under reduced
pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic
phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude
product was purified by column chromatography on silica gel (5% 2-propanol/CH$_2$Cl$_2$) to

give the diethylphosphonate (63 mg, 49%, **GS 16573**) as a white solid: ^{1}H NMR (CDCl$_3$) δ
7.65 (d, J = 8.7Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 6.84 (d, J = 8.4 Hz,
2H), 5.06 (broad, s, 1H), 4.80 (d, J = 7.5 Hz, 1H), 4.19 (m, 6H), 3.83 (s, 3H), 3.80-3.70 (m,
6H), 3.09-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 1.32 (t, J = 7.5 Hz, 6H), 0.86 (d, J = 6.6
5   Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31}P NMR δ 17.8.

Example 5

Dibenzylphosphonate 6: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was
added Cs$_2$CO$_3$ (137 mg, 0.42 mmol) and triflate (165 mg, 0.39 mmol). The reaction mixture
10   was stirred at room temperature for 6 h and the solvent was evaporated under reduced
pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic
phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude
product was purified by column chromatography on silica gel (5% 2-propanol/CH$_2$Cl$_2$) to
give the dibenzylphosphonate (130 mg, 84%, **GS 16574**) as a white solid: ^{1}H NMR (CDCl$_3$)
15   δ 7.65 (d, J = 9 Hz, 2H), 7.30 (m, 10H), 7.08 (d, J = 8.4Hz, 2H), 6.94 (d, J = 9 Hz, 2H), 6.77
(d, J = 8.7 Hz, 2H), 5.16-5.04 (m, 5H), 4.80 (d, J = 8.1 Hz, 1H), 4.16 (d, J = 10.2 Hz, 2H),
3.82 (s, 3H), 3.75-3.71 (m, 6H), 3.10-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 0.86 (d, J =
6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); [31] P NMR (CDCl$_3$) δ 18.8.

20   Example 6

Phosphonic Acid 7: To a solution of 6 (66 mg, 0.08 mmol) in EtOH (3 mL) was added 10%
Pd/C (12 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room
temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate
was concentrated under reduced pressure and triturated with EtOAc to give the phosphonic
25   acid (40 mg, 78%, **GS 16575**) as a white solid.

Example 7

Carbonate 8: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (2 g, 22.7 mmol) in CH$_3$CN
(50 mL) was added triethylamine (6.75 mL, 48.4 mmol) and N,N'-disuccinimidyl carbonate
30   (6.4 g, 25 mmol). The reaction mixture was stirred at room temperature for 5 h and
concentrated under reduced pressure. The residue was partitioned between EtOAc and H$_2$O.
The organic phase was dried with Na$_2$SO$_4$, filtered, and concentrated under reduced pressure.
The crude product was purified by column chromatography on silica gel (EtOAc as eluant)

followed by recrystallization (EtOAc/hexane) to give the carbonate (2.3 g, 44%) as a white solid.

Example 8

5   Carbamate 9: To a solution of 1 (0.218 g, 0.42 mmol) and 8 (0.12 g, 0.53 mmol) in CH_3CN (3 mL) at room temperature was added N, N-diisopropylethylamine (0.11 mL, 0.63 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product

10   was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.176 g, 66%) as a white solid.

Example 9

Phenol 10: To a solution of 9 (0.176 g, 0.28 mmol) in EtOH (10 mL) was added 10% Pd/C

15   (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.151 g, **GS 10**) in quantitative yield.

Example 10

20   Diethylphosphonate 11: To a solution of phenol 10 (60 mg, 0.11 mmol) in THF (3 mL) was added Cs_2CO_3 (72 mg, 0.22 mmol) and triflate (66 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude

25   product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the diethylphosphonate (38 mg, 49%, **GS 11**) as a white solid.

Example Section J

Example 1

Triflate 1: To a solution of A (4 g, 6.9 mmol) in THF (30 mL) and CH$_2$Cl$_2$ (10 mL) was
5   added Cs$_2$CO$_3$ (2.7 g, 8 mmol) and N-phenyltrifluoromethanesulfonimide (2.8 g, 8.0 mmol)
and stirred at room temperature for 16 h. The reaction mixture was concentrated under
reduced pressure. The residue wsa partitioned between CH$_2$Cl$_2$ and saturated brine twice.
The organic phase was dried over sodium sulfate and used for next reaction without further
purification.
10

Example 2

Aldehyde 2: A solution of crude above triflate 1 (~6.9 mmol) in DMF (20 mL) was degassed
(high vacumn for 5 min, argon purge, repeat 3 times). To this solution were quickly added
Pd(OAc)$_2$ (120 mg, 266 µmol) and bis(diphenylphosphino-propane (dppp ,220 mg, 266
15   µmol), and heated to 70°C. To this reaction mixture was rapidly introduced carbon
monoxide, and stirred at room temperature under an atmopheric pressure of carbon
monoxide, followed by slow addition of TEA (5.4 mL, 38 mmol) and triethylsilane (3 mL, 18
mmol). The resultant mixture was stirred at 70°C for 16 h, then cooled to room temperature,
concentrated under reduced pressure, partitioned between CH$_2$Cl$_2$ and saturated brine. The
20   organic phase was concentrated under reduced pressure and purified on silica gel column to
afford aldehyde 2 (2.1 g, 51%) as white solid.

Example 3

Compounds 3a-3e: Respresentative Procedure, 3c: A solution of aldehyde 2 (0.35 g, 0.59
25   mmol), L-alanine isopropyl ester hydrochloride (0.2 g, 1.18 mmol), glacial acetic acid (0.21
g, 3.5 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 16 h,
followed by addition of sodium cyanoborohydride (0.22 g, 3.5 mmol) and methanol (0.5 mL).
The resulting solution was stirred at room temperature for one h. The reaction mixture was
washed with sodium bicarbonate solution, saturated brine, and chromatographed on silica gel
30   to afford 3c (0.17 g, 40%). ^{1}H NMR (CDCl$_3$): δ 7.72 (d, 2H), 7.26 (d, 2H), 7.20 (d, 2H), 7.0
(d, 2H), 5.65 (d, 1H), 4.90-5.30 (m, 3H), 3.53-4.0 (m overlapping s, 13H), 3.31 (q, 1H),
2.70-3.20 (m, 7H), 1.50-1.85 (m, 3H), 1.25-1.31 (m, 9H), 0.92 (d, 3H), 0.88 (d, 3H). MS: 706
(M + 1).

Compound	R₁	R₂	Amino Acid
3a	Me	Me	Ala
3b	Me	Et	Ala
3c	Me	iPr	Ala
3d	Me	Bn	Ala
3e	iPr	Et	Val

Example 4

Sulfonamide 1: To a solution of crude amine A (1 g, 3 mmol) in CH_2Cl_2 was added TEA

(0.6 g, 5.9 mmol) and 3-methoxybenzenesulfonyl chloride (0.6 g, 3 mmol). The resulting

solution was stirred at room temperature for 5 h, and evaporated under reduced pressure. The

residue was chromatographed on silica gel to afford sulfonamide 1 (1.0 g, 67%).

Example 5

Amine 2: To a 0°C cold solution of sulfonamide 1 (0.85 g, 1.6 mmol) in CH_2Cl_2 (40 mL)

was treated with BBr_3 in CH_2Cl_2 (10 mL of 1 M solution, 10 mmol). The solution was stirred

at 0°C 10 min and then warmed to room temperature and stirred for 1.5 h. The reaction

mixture was quenched with CH_3OH, concentrated under reduced pressure, azeotroped with

CH_3CN three times. The crude amine 2 was used for next reaction without further

purification.

Example 6

Carbamate 3: A solution of crude amine 2 (0.83 mmol) in CH_3CN (20 mL) and was treated

with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (245 mg, 0.83

mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-

dimethylaminopyridine (202 mg, 1.7 mmol). After stirring for 16 h at room temperature, the

reaction solvent was evaporated under reduced pressure and the residue was partitioned

between CH_2Cl_2 and saturated $NaHCO_3$ three times. The organic phase was evaporated

under reduced pressure. The residue was purified by chromatography on silica gel affording

the carbamate 3 (150 mg, 33%) as a solid.

Example 7

Diethylphosphonate 4: To a solution of carbamate 3(30 mg, 54 μmol) in THF (5 mL) was added Cs$_2$CO$_3$ (54 mg, 164 μmol) and triflate # (33 mg, 109 μmol). After stirring the reaction mixture for 30 min at room temperature, additional Cs$_2$CO$_3$ (20 mg, 61 μmol) and triflate (15 mg, 50 μmol) were added and the mixture was stirred for 1 more hour. The

5 reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH$_2$Cl$_2$ and water. The organic phase was dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel and repurified by HPLC (50% CH$_3$CN-50% H$_2$O on C18 column) to give the diethylphosphonate 4 (15 mg, 39%). ^{1}H NMR (CDCl$_3$): δ 7.45 (m, 3H), 7.17-7.30 (m, 6H), 5.64 (d, 1H), 5.10 (d, 1H), 5.02

10 (q, 1H), 4.36 (d, 2H), 4.18-4.29 (2 q overlap, 4H), 3.60-3.98 (m, 7H), 2.70-3.10 (m, 7H), 1.80-1.90 (m, 1H), 1.44-1.70 (m, 2H + H2O), 1.38 (t, 6H), 0.94 (d, 3H), 0.90 (d, 3H). ^{31}P NMR (CDCl$_3$): 18.7 ppm; MS (ESI) 699 (M + H).

Example 8

15 Dibenzylphosphonate 5: To a solution of carbamate 3 (100 mg, 182 μmol) in THF (10 mL) was added Cs$_2$CO$_3$ (180 mg, 550 μmol) and dibenzylhydroxymethyl phosphonate triflate, Section A, Scheme 2, Compound 9, (150 mg, 360 μmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH$_2$Cl$_2$ and water. The organic phase was dried

20 (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was purified by HPLC (50% CH$_3$CN-50% H$_2$O on C18 column) to give the dibenzylphosphonate 5 (110 mg, 72%). ^{1}H NMR (CDCl$_3$): δ 7.41 (d, 2H), 7.35 (s, 10 H), 7.17-7.30 (m, 6H), 7.09-7.11 (m, 1H), 5.64 (d, 1H), 4.90-5.15 (m, 6H), 4.26 (d, 2H), 3.81-3.95 (m, 4H), 3.64-3.70 (m, 2H), 2.85-3.25 (m, 7H), 1.80-1.95 (m, 1H), 1.35-1.50 (m, 1H), 0.94 (d, 3H), 0.91 (d, 3H). ^{31}P

25 NMR (CDCl$_3$) δ 19.4 ppm; MS (ESI): 845 (M + Na), 1666 (2M + Na).

Example 9

Phosphonic acid 6: A solution of dibenzylphosphonate 5 (85 mg, 0.1 mmol) was dissolved in MeOH (10 mL) treated with 10% Pd/C (40 mg) and stirred under H$_2$ atmosphere (balloon)

30 overnight. The reaction was purged with N$_2$, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (67 mg, quantitatively). ^{1}H NMR (CD$_3$OD): δ 7.40-7.55 (m, 3H), 7.10-7.35 (m, 6H), 5.57

(d, 1H), 4.32 (d, 2H), 3.90-3.95 (m, 1H), 3.64-3.78 (m, 5H), 3.47 (m, 1H), 2.85-3.31 (m, 5H), 2.50-2.60 (m, 1H), 2.00-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.34 (m, 1H), 0.9 (d, 3H), 0.90 (d, 3H). ^{31}P NMR (CD$_3$OD): 16.60 ppm; MS (ESI): 641 (M – H).

5   Example 10

Sulfonamide 1: To a solution of crude amine A (0.67 g, 2 mmol) in CH$_2$Cl$_2$ (50 mL) was added TEA (0.24 g, 24 mmol) and crude 3-acetoxy-4-methoxybenzenesulfonyl chloride (0.58 g, 2.1 mmol, was prepared according to Kratzl et al., Monatsh. Chem.1952, 83, 1042-1043), and the solution was stirred at room temperature for 4 h, and evaporated under reduced

10   pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (0.64 g, 54%). MS: 587 (M + Na), 1150 (2M + Na)

Phenol 2: Sulfonamide 1 (0.64 g, 1.1 mmol) was treated with saturated NH$_3$ in MeOH (15 mL) at room temperature for 15 min., then evaporated under reduced pressure. The residue

15   was purified on silica gel column to afford phenol 2 (0.57 g, 96%).

Example 11

Dibenzylphosphonate 3a: To a solution of phenol 2 (0.3 g, 0.57 mmol) in THF (8 mL) was added Cs$_2$CO$_3$ (0.55 g, 1.7 mmol)) and dibenzylhydroxymethyl phosphonate triflate (0.5 g,

20   1.1 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH$_2$Cl$_2$ and saturated ammonium chloride aqueous solution. The organic phase was dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (40% EtOAc/ 60% hexane) to give the dibenzylphosphonate 3a (0.36 g, 82%). ^{1}H NMR (CDCl$_3$): δ 7.20-7.40

25   (m, 17H), 6.91 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.58-4.70 (m, 1H), 4.34 (d, 2H), 3.66-3.87 (m + s, 5H), 2.85-3.25 (m, 6H), 1.80-1.95 (m, 1H), 1.58 (s, 9H), 0.86-0.92 (2d, 6H).

Example 12

30   Diethylphosphonate 3b: To a solution of phenol 2 (0.15 g, 0.28 mmol) in THF (4 mL) was added Cs$_2$CO$_3$ (0.3 g, 0.92 mmol)) and diethylhydroxymethyl phosphonate triflate (0.4 g, 1.3 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$ aqueous

solution. The organic phase was dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (1% CH$_3$OH-CH$_2$Cl$_2$) to give the diethylphosphonate 3b (0.14 g, 73%).

5   ## Example 13

Amine 4a: To a solution of 3a (0.35 g, 0.44 mmol) in CH$_2$Cl$_2$ (10 mL) was treated with TFA (0.75 g, 6.6 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH$_3$CN twice, dried to afford crude amine 4a. This crude 4a was used for next reaction without further purification.

10

Example 14

Amine 4b: To a solution of 3b (60 mg, 89 μmol) in CH$_2$Cl$_2$ (1 mL) was treated with TFA (0.1 mL, 1.2 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH$_3$CN twice, dried to afford crude amine 4b (68 mg). This crude

15   4b was used for next reaction without further purification.

Example 15

Carbamate 5a: An ice-cold solution of crude amine 4a (0.44 mmol) in CH$_3$CN (10 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate

20   (120 mg, 0.4 mmol) and N,N-dimethylaminopyridine (DMAP, 110 mg, 0.88 mmol). After 4 h, more DMAP (0.55 g, 4.4 mmol) was added to the reaction mixture. After stirring for 1.5 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica

25   gel affording the crude carbamate 5a (220 mg) containing some p-nitrophenol. The crude 5a was repurified by HPLC (50% CH$_3$CN /50% H$_2$O) to afford pure carbamate 5a (176 mg, 46%, 2 steps). ^{1}H NMR (CDCl$_3$): δ 7.20-7.36 (m, 1H), 6.94 (d, 1H), 5.64 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.90-5.10 (m, 1H), 4.90 (d, 1H), 4.34 (d, 2H), 3.82-3.91 (m + s, 6H), 3.63-3.70 (m, 3H), 2.79-3.30 (m, 7H), 1.80-1.90 (m, 1H), 1.40-1.50 (m, 1H), 0.94 (d, 3H),

30   0.89 (d, 3H). ^{31}P NMR (CDCl$_3$): 17.2 ppm.

Example 16

Carbamate 5b: An ice-cold solution of crude amine 4b (89 μmol)) in CH₃CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (26mg, 89 μmol) and N,N-dimethylaminopyridine (DMAP, 22 mg, 0.17 mmol). After 1 h at 0°C, more DMAP (10 mg. 82 μmol) was added to the reaction mixture. After stirring for 2 h at
5 room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH₂Cl₂ and saturated NaHCO₃. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC (C18 column, 45% CH₃CN/55% H₂O) to afford pure carbamate 5b (18.8 mg, 29%, 3 steps). ¹H NMR (CDCl₃): δ 7.38 (d, 2H), 7.20-7.36 (m, 6H), 7.0 (d, 1H), 5.64 (d, 1H), 4.96-5.03 (m, 2H), 4.39 (d, 2H),
10 4.20-4.31 (2q overlap, 4H) 3.80-4.00 ((s overlap with m, 7H), 3.60-3.73 (m, 2H), 3.64-3.70 (m, 2H), 2.85-3.30 (m, 7H), 1.80-1.95 (m, 1H), 1.55-1.75 (m, 1H), 1.35-1.50 (s overlap with m, 7H), 0.94 (d, 3H), 0.88 (d, 3H). ³¹P NMR (CDCl₃): 18.1ppm.

Example 17

15 Phosphonic acid 6: A solution of dibenzylphosphonate 5a (50 mg, 58 μmol) was dissolved in MeOH (5 mL) and EtOAc (3 mL) and treated with 10% Pd/C (25 mg) and was stirred at room temperature under H₂ atmosphere (balloon) for 8 h. The catalyst was filtered off. The filtrate was concentrated and redissolved in MeOH (5 mL), treated with 10% Pd/C (25 mg) and was stirred at room temperature under H₂ atmosphere (balloon) overnight. The catalyst
20 was filtered off. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (38 mg, quantitatively). ¹H NMR (CD₃OD): δ 7.42 (m, 1H), 7.36 (s, 1H), 7.10-7.25 (m, 6H), 5.58 7 (d, 1H), 4.32 (d, 2H), 3.90 (s, 3H), 3.60-3.80 (m, 6H), 3.38 (d, 1H), 2.85-3.25 (m, 5H), 2.50-2.60 (m, 1H), 1.95-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.40 (m, 1H), 0.93(d, 3H), 0.89 (d, 3H). ³¹P NMR (CD₃OD): 14.8 ppm; MS (ESI): 671 (M – H).
25

Example 18

Amine 7: To a 0°C cold solution of diethylphosphonate 3b (80 mg, 0.118 mmol) in CH₂Cl₂ was treated with BBr₃ in CH₂Cl₂ (0.1 mL of 1 M solution, 1 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 3 h. The reaction
30 mixture was concentrated under reduced pressure. The residue was redissolved in CH₂Cl₂ (containing some CH₃OH, concentrated, azeotroped with CH₃CN three times. The crude amine 7 was used for next reaction without further purification.

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Example 19

Carbamate 8: An ice-cold solution of crude amine 7 (0.118 mmol) in CH₃CN (5 mL) and

was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (35

5   mg, 0.118 mmol) and N,N-dimethylaminopyridine (29 mg, 0.24mmol), warmed to room

temperature. After stirring for 1 h at room temperature, more DMAP (20 mg, 0.16 mmol)

was added to reaction mixture. After 2 h stirred at room temperature, the reaction solvent

was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and

saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue

10   was purified by HPLC on C18 (CH_3CN-55%H_2O) to afford the desired carbamate 8 (11.4

mg, 13.4%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 7.20-7.40 (m, 7H), 7.00 (d, 1H), 5.64

(d, 1H), 5.00-5.31 (m, 2H), 4.35 (d, 2H), 4.19-4.30 (2q overlap, 4H), 3.80-4.00 (m, 4H), 3.68-

3.74 (m, 2H), 3.08-3.20 (m, 3H), 2.75-3.00 (m, 4H), 1.80-1.90 (m, 1H), 1.55-1.75 (m, 1H),

1.38 (t, 6H), 0.91 (2d overlap, 6H). ^{31}P NMR (CD_3OD): δ19.5 ppm.

15

Example Section K

Example 1

Monophenyl-monolactate 3: A mixture of monoacid 1 (0.500 g, 0.7 mmol), alcohol 2 (0.276

5   g, 2.09 mmol) and dicyclohexylcarbodiimide (0.431 g, 2.09 mmol) in dry pyridine (4 mL)

was placed into a 70°C oil bath and heated for two hours. The reaction was monitored by

TLC assay (SiO$_2$, 70% ethyl acetate in hexanes as eluent, product R$_f$ = 0.68, visualization by

UV). The reaction contents were cooled to ambient temperature with the aid of a cool bath

and diluted with dichloromethane (25 mL). TLC assay may show presence of starting

10   material. The diluted reaction mixture was filtered to remove solids. The filtrate was then

cooled to 0°C and charged with 0.1 N HCl (10 mL). The pH 4 mixture was stirred for 10

minutes and poured into separatory funnel to allow the layers to separate. The lower organic

layer was collected and dried over sodium sulfate. The drying agent was filtered off and the

filtrate concentrated to an oil via rotary evaporator (< 30°C warm bath). The crude product

15   oil was purified on pretreated silica gel (deactivated using 10% methanol in dichloromethane

followed by rinse with 60% ethyl acetate in dichloromethane). The product was eluted with

60% ethyl acetate in dichloromethane to afford the product monophenyl-monolactate 3 as a

white foam (0.497 g, 86% yield). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.00 (m, 14H), 5.65

(d, 1H), 5.20-4.90 (m, 4H), 4.70 (d, 1H), 4.55-4.50 (m, 1H), 4.00-3.80 (m, 4H), 3.80-3.60 (m,

20   3H), 3.25-2.75 (m, 7H), 1.50 (d, 3H), 1.30-1.20 (m, 7H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P

NMR (CDCl$_3$) δ 16.2, 13.9.

Example 2

Monophenyl-monoamidate 5: A mixture of monoacid 1 (0.500 g, 0.70 mmol), amine

25   hydrochloride 4 (0.467 g, 2.78 mmol) and dicyclohexylcarbodiimide (0.862 g, 4.18 mmol) in

dry pyridine (8 mL) was placed into a 60°C oil bath, and heated for one hour (at this

temperature, product degrades if heating continues beyond this point). The reaction was

monitored by TLC assay (SiO$_2$, 70% ethyl acetate in hexanes as eluent, product R$_f$ = 0.39,

visualization by UV). The contents were cooled to ambient temperature and diluted with

30   ethyl acetate (15 mL) to precipitate a white solid. The mixture was filtered to remove solids

and the filtrate was concentrated via rotary evaporator to an oil. The oil was diluted with

dichloromethane (20 mL) and washed with 0.1 N HCl (2 x 20 mL), water (1 x 20 mL) and

dilute sodium bicarbonate (1 x 20 mL). The organic layer was dried over sodium sulfate,

filtered, and concentrated to an oil via rotary evaporator. The crude product oil was dissolved in dichloromethane (10 mL). Hexane was slowly charged to the stirring solution until cloudiness persisted. The cloudy mixture was stirred for a few mintues until TLC assay showed that the dichloromethane/hexane layer contained no product. The

5 dichloromethane/hexanes layer was decanted and the solid was further purified on silica gel first pretreated with 10% methanol in ethyl acetate and rinsed with 50% ethyl acetate in hexanes. The product 5 was eluted with 50% ethyl acetate in hexanes to afford a white foam (0.255 g, 44% yield) upon removal of solvents. ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.15 (m, 10H), 7.15-7.00 (t, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 3H), 4.50-4.35 (m, 2H), 4.25-4.10

10 (m, 1H), 4.00-3.60 (m, 8H), 3.20-2.75 (m, 7H), 1.40-1.20 (m, 11H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 19.1, 18.0.

Example 3

Bisamidate 8: A solution of triphenylphosphine (1.71 g, 6.54 mmol) and aldrithiol (1.44 g,

15 6.54 mmol) in dry pyridine (5 mL), stirred for at least 20 minutes at room temperature, was charged into a solution of diacid 6 (1.20 g, 1.87 mmol) and amine hydrochloride 7 (1.30 g, 7.47 mmol) in dry pyridine (10 mL). Diisopropylethylamine (0.97 g, 7.48 mmol) was then added to this combined solution and the contents were stirred at room temperature for 20 hours. The reaction was monitored by TLC assay (SiO$_2$, 5:5:1 ethyl

20 acetate/hexanes/methanol as eluent, product R$_f$ = 0.29, visualization by UV). The reaction mixture was concentrated via rotary evaporator and dissolved in dichloromethane (50 mL). Brine (25 mL) was charged to wash the organic layer. The aqueous layer was back extracted with dichloromethane (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford an oil. The crude product oil

25 was purified on silica gel using 4% isopropanol in dichloromethane as eluent. The combined fractions containing the product may have residual amine contamination. If so, the fractions were concentrated via rotary evaporator and further purified by silica gel chromatography using a gradient of 1:1 ethyl acetate/hexanes to 5:5:1 ethyl acetate/hexanes/methanol solution as eluent to afford the product 8 as a foam (0.500 g, 30% yield).

30

Example 4

Diacid 6: A solution of dibenzylphosphonate 9 (8.0 g, 9.72 mmol) in ethanol (160 mL) and ethyl acetate (65 mL) under a nitrogen atmosphere and at room temperature was charged 10%

Pd/C (1.60 g, 20 wt%). The mixture was stirred and evacuated by vacuum and purged with

hydrogen several times. The contents were then placed under atmospheric pressure of

hydrogen via a balloon. The reaction was monitored by TLC assay (SiO$_2$, 7:2.5:0.5

dichloromethane/methanol/ammonium hydroxide as eluent, product R$_f$ = 0.05, visualization

5   by UV) and was judged complete in 4 to 5 hours. The reaction mixture was filtered through a

pad of celite to remove Pd/C and the filter cake rinsed with ethanol/ethyl acetate mixture (50

mL). The filtrate was concentrated via rotary evaporation followed by several co-

evaporations using ethyl acetate (3 x 50 mL) to remove ethanol. The semi-solid diacid 6, free

of ethanol, was carried forward to the next step without purification.

10

Example 5

Diphenylphosphonate 10: To a solution of diacid 6 (5.6 g, 8.71 mmol) in pyridine (58 mL) at

room temperature was charged phenol (5.95 g, 63.1 mmol). To this mixture, while stirring,

was charged dicyclohexylcarbodiimide (7.45 g, 36.0 mmol). The resulting cloudy, yellow

15   mixture was placed in a 70-80°C oil bath. The reaction was monitored by TLC assay (SiO$_2$,

7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diacid R$_f$ = 0.05,

visualization by UV for the disappearance of starting material. SiO$_2$, 60% ethyl acetate in

hexanes as eluent, diphenyl R$_f$ = 0.40, visualization by UV) and was judged complete in 2

hours. To the reaction mixture was charged isopropyl acetate (60 mL) to produce a white

20   precipitation. The slurry was filtered through a pad of celite to remove the white precipitate

and the filter cake rinsed with isopropyl acetate (25 mL). The filtrate was concentrated via

rotary evaporator. To the resulting yellow oil was charged a premixed solution of water (58

mL) and 1N HCl (55 mL) followed by isopropyl acetate (145 mL). The mixture was stirred

for one hour in an ice bath. After separating the layers, the aqueous layer was back extracted

25   with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate,

filtered, and concentrated via rotary evaporator. The crude product oil was purified by silica

gel column chromatography using 50% ethyl acetate in hexanes as eluent to afford the

product 10 as a white foam (3.52 g, 51% yield). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.20

(m, 15H), 7.10 (d, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 2H), 4.65 (d, 2H), 4.00-3.80 (m, 4H),

30   3.75-3.65 (m, 3H), 3.25-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.70-1.60 (m, 1H), 1.50-1.40 (m,

1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 10.9.

Example 6

Monophenyl 1: To a solution of diphenyl 10 (3.40 g, 4.28 mmol) in acetonitrile (170 mL) at 0°C was charged 1N sodium hydroxide (4.28 mL). The reaction was monitored by TLC assay (SiO$_2$, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diphenyl R$_f$ = 0.65, visualization by UV for the disappearance of starting material. Product

5   monophenyl R$_f$ = 0.80, visualization by UV). Additional 1N NaOH was added (if necessary) until the reaction was judged complete. To the reaction contents at 0°C was charged Dowex H$^+$ (Dowex 50WX8-200) (4.42 g) and stirred for 30 minutes at which time the pH of the mixture reached pH 1 (monitored by pH paper). The mixture was filtered to remove the Dowex resin and the filtrate was concentrated via rotary evaporation (water bath < 40°C).

10   The resulting solution was co-evaporated with toluene to remove water (3 x 50 mL). The white foam was dissolved in ethyl acetate (8 mL) followed by slow addition of hexanes (16 mL) over 30 minutes to induce precipitation. A premixed solution of 2:1 hexnaes/ethyl acetate solution (39 mL) was charged to the precipitated material and stirred. The product 1 was filtered and rinsed with premixed solution of 2:1 hexanes/ethyl acetate solution (75 mL)

15   and dried under vacuum to afford a white powder (2.84 g, 92% yield). ^{1}H NMR (CD$_3$OD) δ 7.80 (d, 2H), 7.40-7.30 (m, 2H), 7.20-7.15 (m, 11H), 5.55 (d, 1H), 4.50 (d, 2H), 3.95-3.85 (m, 1H), 3.80-3.60 (m, 5H), 3.45 (bd, 1H), 3.25-3.15 (m, 2H), 3.00-2.80 (m, 3H), 2.60-2.45 (m, 1H), 2.10-1.95 (m, 2H), 1.85-1.60 (m, 2H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 13.8. The monophenyl product 1 is sensitive to silica

20   gel. On contact with silica gel 1 converts to an unknown compound possessing ^{31}P NMR chemical shift of 8 ppm. However, the desired monophenyl product 1 can be regenerated by treatment of the unknown compound with 2.5 M NaOH in acetonitrile at 0°C for one hour followed by Dowex H$^+$ treatment as described above.

25   Example 7

Dibenzylphosphonate 9: To a solution of phenol 11 (6.45 g, 11.8 mmol) in tetrahydrofuran (161 mL) at room temperature was charged triflate reagent 12 (6.48 g, 15.3 mmol). Cesium carbonate (11.5 g, 35.3 mmol) was added and the mixture was stirred and monitored by TLC assay (SiO$_2$, 5% methanol in dichloromethane as eluent, dibenzyl product R$_f$ = 0.26,

30   visualization by UV or ninhydrin stain and heat). Additional Cs$_2$CO$_3$ was added until the reaction was judged complete. To the reaction contents was charged water (160 mL) and the mixture extracted with ethyl acetate (2 x 160 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford a viscous oil.

The crude oil was purified by silica gel column chromatography using a gradient of 100% dichloromethane to 1% methanol in dichloromethane to afford product 9 as a white foam (8.68 g, 90% yield). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 16H), 6.95 (d, 2H), 5.65 (d, 1H), 5.20-4.90 (m, 6H), 4.25 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.20-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.30-1.20 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 19.1.

Example 7a

Hydroxyphenylsulfonamide 14: To a solution of methoxyphenylsulfonamide 13 (35.9 g, 70.8 mmol) in dichloromethane (3.5 L) at 0°C was charged boron tribromide (1M in DCM, 40.1 mL, 425 mmol). The reaction content was allowed to warm to room temperature, stirred over two hours, and monitored by TLC assay (SiO$_2$, 10% methanol in dichloromethane as eluent, dibenzyl product R_f = 0.16, visualization by UV). To the contents at 0°C was slowly charged propylene oxide (82 g, 1.42 mmol). Methanol (200 mL) was added and the reaction mixture was concentrated via rotary evaporator to afford a viscous oil. The crude product mixture was purified by silica gel column chromatography using 10% methanol in dichloromethane to afford the product 14 as a foam (22 g, 80% yield). ^{1}H NMR (DMSO) δ 7.60 (d, 2H), 7.30-7.20 (m, 5H), 6.95 (d, 2H), 3.90-3.75 (m, 1H), 3.45-3.20 (m, 5H), 3.00-2.55 (m, 5H), 2.50-2.40 (m, 1H), 1.95-1.85 (m, 1H), 0.85 (d, 3H), 0.80 (d, 3H).

Example 8

Cisfuran carbamate 16: To a solution of amine 14 (20.4 g, 52.0 mmol) in acetonitrile (600 mL) at room temperature was charged dimethylaminopyridine (13.4 g, 109 mmol) followed by cisfuran p-nitrophenylcarbonate reagent 15 (14.6 g, 49.5 mmol). The resulting solution was stirred at room temperature for at least 48 hours and monitored by TLC assay (SiO$_2$, 10% methanol in dichloromethane as eluent, cisfuran product R_f = 0.34, visualization by UV). The reaction mixture was concentrated via rotary evaporator. The crude product mixture was purified by silica gel column chromatography using a gradient of 60% ethyl acetate in hexanes to 70% ethyl acetate in hexanes to afford the product 16 as a solid (18.2 g, 64% yield). ^{1}H NMR (DMSO) δ 10.4 (bs, 1H), 7.60 (d, 2H), 7.30-7.10 (m, 6H), 6.95 (d, 2H), 5.50 (d, 1H), 4.85 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.65-3.50 (m, 4H), 3.30 (d, 1H), 3.05-2.95 (m, 2H), 2.80-2.65 (m, 3H), 2.50-2.40 (m, 1H), 2.00-1.90 (m, 1H), 1.45-1.20 (m, 2H), 0.85 (d, 3H), 0.80 (d, 3H).

Example Section L

Example 1

Monobenzyl phosphonate 2 A solution of dibenzylphosphonate 1(150 mg, 0.175mmol) was

5   dissolved in toluene (1 mL), treated with DABCO (20 mg, 0.178 mmol) and was refluxed

under N2 atmosphere (balloon) for 3 h. The solvent was removed and the residual was

dissolved in aqueous HCl (5%). The aqueous layer was extracted with ethyl acetate and the

organic layer was dried over sodium sulfate. After evaporation to yield the monobenzyl

phosphonate 2 (107 mg, 80%) as a white powder. ^{1}H NMR (CD$_3$OD) δ 7.75 (d, J = 5.4 Hz,

10   2H), 7.42-7.31 (m, 5H) 7.16 (d, J = 5.4 Hz, 2H), 7.01 (d, J = 5.4 Hz, 2H), 6.86 (d, J = 5.4 Hz,

2H), 5.55 (d, J = 3.3 Hz, 1H), 5.14 (d, J = 5.1 Hz, 2H), 4.91 (m, 1H), 4.24-3.66 (m

overlapping s, 11H), 3.45 (m, 2H), 3.14-2.82 (m, 6H), 2.49 (m, 1H), 2.01 (m, 1H), 1.51-1.34

(m, 2H), 0.92 (d, J = 3.9 Hz, 3H), 0.87 (d, J = 3.9 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 20.5; MS

(ESI) 761 (M-H).

15

Example 2

Monobenzyl, ethyl phosphonate 3 To a solution of monobenzyl phosphonate 2 (100 mg, 0.13

mmol) in dry THF (5 mL) at room temperature under N$_2$ was added Ph$_3$P (136 mg, 0.52

mmol) and ethanol (30 µL, 0.52 mmol). After cooled to 0°C, DEAD (78µL, 0.52 mmol) was

20   added. The mixture was stirred for 20 h at room temperature. The solvent was evaporated

under reduced pressure and the residue was purified by using chromatograph on silica gel

(10% to 30% ethyl acetate / hexane) to afford the monobenzyl, ethyl phosphonate 3 (66 mg,

64%) as white solid. ^{1}H NMR (CDCl$_3$) 7.70 (d, J = 8.7 Hz, 2H), 7.43-7.34 (m, 5H) 7.14 (d,

J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.56 (d, J = 5.4 Hz, 1H),

25   5.19 (d, J = 8.7 Hz, 2H), 5.00 (m, 2H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.76 (m, 7H),

1.82-1.54 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H);

^{31}P NMR (CDCl$_3$) δ 19.8; MS (ESI) 813 (M+Na).

Example 3

30   Monoethyl phosphonate 4 A solution of monobenzyl, ethyl phosphonate 3 (60 mg) was

dissolved in EtOAc (2 mL), treated with 10% Pd/C (6 mg) and was stirred under H$_2$

atmosphere (balloon) for 2h. The catalyst was removed by filtration through celite. The

filtered was evaporated under reduced pressure, the residue was triturated with ether and the

solid was collected by filtration to afford the monoethyl phosphonate 4 (50 mg, 94%) as white solid. ^{1}H NMR (CD$_3$OD) 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.90 (m, 1H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.50 (m, 7H), 1.98(m, 1H), 1.56 (m, 2H), 1.33 (t, J = 6.9 Hz, 3H), 0.92 (d, J = 6.6Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 18.7; MS (ESI) 700 (M-H).

Example 4

Monophenyl, ethyl phosphonate 5 To a solution of phosphonic acid 11 (800 mg, 1.19 mmol) and phenol (1.12 g, 11.9 mmol) in pyridine (8 mL) was added ethanol (69 µL, 1.19 mmol) and 1, 3-dicyclohexylcarbodiimide (1g, 4.8 mmol). The solution was stirred at 70°C for 2h. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate (10 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate and the organic phase was separated and washed with brine, dried over MgSO4, filtered and concentrated. The residue was purified by chromatography on silica gel to give monophenyl, ethyl phosphonate 5 (600 mg, 65%) as white solid. ^{1}H NMR (CDCl$_3$) 7.72 (d, J = 9 Hz, 2H), 7.36-7.18 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 9Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.00 (m, 2H), 4.34 (m, 4H), 3.94-3.67 (m overlapping s, 9H), 3.18-2.77 (m, 7H), 1.82-1.54 (m, 3H), 1.36 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 16.1; MS (ESI) 799 (M+Na).

Example 5

Sulfonamide 6 To a suspension of epoxide 5 (3 g, 8.12 mmol) in 2-propanol (30 mL) was added isobutylamine (8 mL, 81.2 mmol) and the solution was stirred at 80°C for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$ (40 mL) and cooled to 0°C. TEA (2.3 mL, 16.3mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (1.8 g, 8.13 mmol) in CH$_2$Cl$_2$ (5 mL) and the solution was stirred for 30 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide 6 (4.6 g, 91%) as an off-white solid. MS (ESI) 650 (M+Na).

Example 6

Phenol 7 A solution of sulfonamide 6 (4.5 g, 7.1 mmol) in CH_2Cl_2 (50 mL) at 0°C was treated with BBr_3 (1M in CH_2Cl_2, 50mL). The solution was stirred at 0°C to room temperature for 48h. CH_3OH (10 mL) was carefully added. The solvent was evaporated

5 under reduced pressure and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase washed with saturated NaCl, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% - $MeOH/CH_2Cl_2$) to give the phenol 7 (2.5 g, 80%) as an off-white solid. MS (ESI) 528 (M+H).

10

Example 7

Carbamate 8 A solution of sulfonamide 7 (2.5 g, 5.7 mmol) in CH_3CN (100 mL) and was treated with proton-sponge (3 g, 14 mmol) and followed by (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (1.7 g, 5.7 mmol) at 0°C. After stirring for 48h at

15 room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 10% HCl. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% $MeOH/CH_2Cl_2$) affording the carbamate 8 (2.1g, 62 %) as a white solid. MS (ESI) 616 (M+Na).

20

Example 8

Diethylphosphonate 9 To a solution of carbamate 8 (2.1 g, 3.5 mmol) in CH_3CN (50 mL) was added Cs_2CO_3 (3.2 g, 9.8 mmol) and diethyltriflate (1.6g, 5.3 mmol). The mixture was stirred at room temperature for 1h. After removed the solvent, the residue was partitioned

25 between EtOAc and saturated NaCl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (1% to 5% MeOH /CH_2Cl_2) to afford the diethylphosphonate 9 as a white solid: ^{1}H NMR (CDCl$_3$) δ 8.35 (d, J = 9 Hz, 2H), 7.96 (d, J = 9 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.18-5.01 (m, 2H), 4.27-4.17 (m, 6H), 3.94-3.67 (m,

30 7H), 3.20-2.73 (m, 7H), 1.92-1.51 (m, 3H), 1.35 (t, J = 7.2 Hz, 6H), 0.88-0.85 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 19.2; MS (ESI) 756 (M+Na).

Example 9

-1343-

Amine 10 A solution of diethylphosphonate 9 (1 g) was dissolved in EtOH (100 mL), treated with 10% Pd/C (300 mg) and was stirred under H_2 atmosphere (balloon) for 3h. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the amine 10 (920 mg, 96%) as a white solid. ^{1}H NMR (CDCl$_3$) ^{1}H NMR (CDCl$_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.13-5.05 (m, 2H), 4.42 (s, 2H), 4.29-4.20 (m, 6H), 4.00-3.69 (m, 7H), 3.00-2.66 (m, 7H), 1.80-1.69 (m, 3H), 1.38 (m, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 6H); ^{31}P NMR (CDCl$_3$) δ 19.4; MS (ESI) 736 (M+Na).

Compound	R$_1$	R$_2$
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Example 10

Synthesis of Bisamidates 16a. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine ethyl ester hydrochloride (84 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16a (90 mg, 72%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 5.1 Hz,, 1H), 5.05 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H), 1.27 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 21.8; MS (ESI) 843 (M+H).

Example 11

Synthesis of Bisamidates 16b. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine n-butyl ester hydrochloride (101 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol)

5   in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16b (100 mg, 74%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H),

10   5.67 (d, J = 5.4 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.11 (t, J = 6.9 Hz, 4H), 3.99-3.71 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.80 (m, 7H), 1.87-1.60 (m, 7H), 1.42 (m, 4H), 0.96-0.88 (m, 12H); ^{31}P NMR (CDCl$_3$) δ 21.8; MS (ESI) 890 (M+H).

Example 12

15   Synthesis of Bisamidates 16j. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-phenylalanine n-butyl ester hydrochloride (155 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 36h at room temperature. The solvent was evaporated

20   under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16j (106 mg, 66%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.31-7.10 (m, 12H), 7.01 (d, J = 9 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.35-3.98 (m., 7H), 3.90-

25   3.61 (m overlapping s, 10H,), 3.19-2.78 (m, 11H), 1.87-1.25 (m, 11H), 0.96-0.88 (m, 12H); ^{31}P NMR (CDCl$_3$) δ 19.3; MS (ESI) 1080 (M+H).

Example 13

Synthesis of Bisamidates 16k. A solution of phosphonic acid 11 (80 mg, 0.12 mmol),

30   ethylamine (0.3 mL,2M in THF, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (109 mg, 0.42 mmol) and 2,2'-dipyridyl disulfide (93 mg, 0.42 mmol) in pyridine (1 mL) stirring for 48h at room temperature. The solvent was evaporated under reduced

pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16k (60 mg, 70%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz , 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05-4.95 (m, 2H), 4.15 (d, J = 9.6 Hz, 2H), 3.99-3.72 (m overlapping s, 9H,), 3.18-2.81 (m, 11H), 2.55 (br, 1H), 1.85-1.65 (m, 3H), 1.18 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 21.6; MS (ESI) 749 (M+Na).

Compound	R$_1$	R$_2$
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh·	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Example 14

Monoamidate 30a (R1 = OPh, R2 = Ala-Me) To a flask was charged with monophenyl phosphonate 29 (75 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and NaHCO$_3$, dried over Na$_2$SO$_4$ filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.01 (m, 2H), 4.30 (m, 2H), 3.97-3.51 (m overlapping s, 12H), 3.20-2.77 (m, 7H), 1.81 (m, 1H), 1.58 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.4 and 19.3; MS (ESI) 856 (M+Na).

Example 15

Monoamidate 30b (R1 = OPh, R2 = Ala-Et) was synthesized in the same manner in 35% yield. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67

(m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl₃) δ 20.4 and 19.3; MS (ESI) 870 (M+Na).

Example 16

Monoamidate 30c (R1 = OPh, R2 = (D)-Ala-iPr) was synthesized in the same manner in 52% yield. Isomer A ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl₃) δ 20.4; MS (ESI) 884 (M+Na). Isomer B ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl₃) δ 19.3; MS (ESI) 884 (M+Na).

Example 17

Monoamidate 30d (R1 = OPh, R2 = Ala-Bu) was synthesized in the same manner in 25% yield. ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 16H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 8H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl₃) δ 20.4 and 19.4; MS (ESI) 898 (M+Na).

Example 18

Monoamidate 30e (R1 = OBn, R2 = Ala-Et) To a flask was charged with monobenzyl phosphonate 2 (76 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and NaHCO₃, dried over Na₂SO₄ filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.13

(d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86-6.80 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.15-5.01 (m, 5H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 23.3 and 22.4; MS (ESI) 884 (M+Na).

Compound	R$_1$	R$_2$
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Example 19

Monolactate 31a (R1 = OPh, R2 = Lac-iPr): To a flask was charged with monophenyl phosphonate 29 (1.5 g, 2 mmol), isopropyl-(s)-lactate (0.88 mL, 6.6 mmol) and 1, 3- dicyclohexylcarbodiimide (1.36 g, 6.6 mmol), then pyridine (15 mL) was added under N$_2$. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / CH$_2$Cl$_2$ 1:5) to give 31a (1.39g, 81%) as a white solid. Isomer A ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.65 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.56-4.44 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13- 2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4; MS (ESI) 885 (M+Na). Isomer B ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.53 -4.41 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 15.3; MS (ESI) 885 (M+Na).

Example 20

Monolactate 31b (R1 = OPh, R2 = Lac-Et) was synthesized in the same manner in 75% yield. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m,

2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

5   Example 21

Monolactate 31c (R1 = OPh, R2 = Lac-Bu) was synthesized in the same manner in 58% yield. Isomer A ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.63 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.56-4.51 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-

10   2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.3; MS (ESI) 899 (M+Na). Isomer B ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.44 -4.39 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m,

15   6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 15.3; MS (ESI) 899 (M+Na).

Example 22

Monolactate 31d (R1 = OPh, R2 = (R)-Lac-Me): To a stirred solution of monophenyl

20   phosphonate 29 (100 mg, 0.13 mmol) in 10 mL of THF at room temperature under N$_2$ was added methyl-(S)-lactate (54 mg, 0.52 mmol) and Ph$_3$P (136 mg g,, 0.52 mmol), followed by DEAD (82µL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31d (33 mg, 30%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7

25   Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 3.95 -3.64 (m overlapping s, 12H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4 and 15.3; MS (ESI) 857 (M+Na).

30   Example 23

Monolactate 31e (R1 = OPh, R2 = (R)-Lac-Et): To a stirred solution of monophenyl phosphonate 29 (50 mg, 0.065 mmol) in 2.5 mL of THF at room temperature under N$_2$ was

added ethyl-(s)-lactate (31 mg, 0.52 mmol) and Ph₃P (68 mg g, 0.26 mmol), followed by
DEAD (41μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and
the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate /
hexane 1:1) to give 31e (28 mg, 50%) as a white solid. ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7
Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.85(m, 2H), 5.63 (m, 1H), 5.19-4.95
(m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77
(m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);
^{31}P NMR (CDCl₃) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

Example 24

Monolactate 32 (R1 = OBn, R2 = (S)-Lac-Bn): To a stirred solution of monobenzyl
phosphonate 2 (76 mg, 0.1 mmol) in 0.5 mL of DMF at room temperature under N₂ was
added benzyl-(s)-lactate (27 mg, 0.15 mmol) and PyBOP (78 mg, 0.15mmol), followed by
DIEA (70μL, 0.4 mmol). After 3 h, the solvent was removed under reduced pressure, and the
resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane
1:1) to give 32 (46 mg, 50%) as a white solid. ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7 Hz, 2H),
7.38-7.44 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (d, J
= 5.1 Hz, 1H), 5.23-4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-
2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR
(CDCl₃) δ 20.8 and 19.6; MS (ESI) 947 (M+Na).

Example 25

Monolactate 33 (R1 = OBn, R2 = (R)-Lac-Bn): To a stirred solution of monobenzyl
phosphonate 2 (76 mg, 0.1 mmol) in 5 mL of THF at room temperature under N₂ was added
benzyl-(s)-lactate (72 mg, 0.4 mmol) and Ph₃P (105 mg g, 0.4mmol), followed by DEAD
(60μL, 0.4 mmol). After 20 h, the solvent was removed under reduced pressure, and the
resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane
1:1) to give 33 (44 mg, 45%) as a white solid. ^{1}H NMR (CDCl₃) δ 7.72 (d, J = 8.7 Hz, 2H),
7.38-7.44 (m, 10H), 7.13 (m, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (m, 1H), 5.23-
4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-
1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl₃) δ 20.8
and 19.6; MS (ESI) 947 (M+Na).

Example 26

Monophosphonic acid 34: A solution of monobenzyllactate 32 (20 mg) was dissolved in
EtOH/ EtOAc (3 mL/1 mL), treated with 10% Pd/C (4 mg) and was stirred under H2

5 atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The
filtered was evaporated under reduced pressure, the residue was triturated with ether and the
solid was collected by filtration to afford the monophosphonic acid 33 (15 mg, 94%) as a
white solid. ^{1}H NMR (CD$_3$OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J
= 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m,

10 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00
(m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR
(CD$_3$OD) δ 18.0; MS (ESI) 767 (M+Na).

Example 27

15 Monophosphonic acid 35: A solution of monobenzyllactate 33(20 mg) was dissolved in
EtOH (3 mL), treated with 10% Pd/C (4 mg) and was stirred under H2 atmosphere (balloon)
for 1h. The catalyst was removed by filtration through celite. The filtered was evaporated
under reduced pressure, the residue was triturated with ether and the solid was collected by
filtration to afford the monophosphonic acid 35 (15 mg, 94%) as a white solid. ^{1}H NMR

20 (CD$_3$OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90
(d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90 -3.65 (m
overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38
(m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 18.0; MS
(ESI) 767 (M+Na).

25

Example 28

Synthesis of Bislactate 36: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) isopropyl-
(S)-lactate (79 mg, 0.66 mmol) was dissolved in pyridine (1 mL) and the solvent was
distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P

30 (137 mg, 0.53 mmol) and 2,2'-dipyridyl disulfide (116 mg, 0.53 mmol) in pyridine (1 mL)
stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and
the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified
product was suspended in ether and was evaporated under reduced pressure to afford

-1351-

bislactate 36 (42 mg, 32%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.05 (m, 3H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 9H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H),1.58 (m, 6H), 1.26 (m, 12H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 21.1; MS (ESI) 923 (M+Na).

Example 29

Triflate derivative 1: A THF-CH$_2$Cl$_2$ solution (30mL-10 mL) of 8 (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative 1.

Aldehyde 2: Crude triflate 1 (4.5 g, 6.9 mmole) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)2 (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added and the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 mL, 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde 2 (2.1 g, 51%). (Hostetler, et al. J. Org. Chem., 1999. 64, 178-185).

Lactate prodrug 4: Compound 4 is prepared as described above procedure for 3a-e by the reductive amination between 2 and 3 with NaBH$_3$CN in 1,2-dichloroethane in the presence of HOAc.
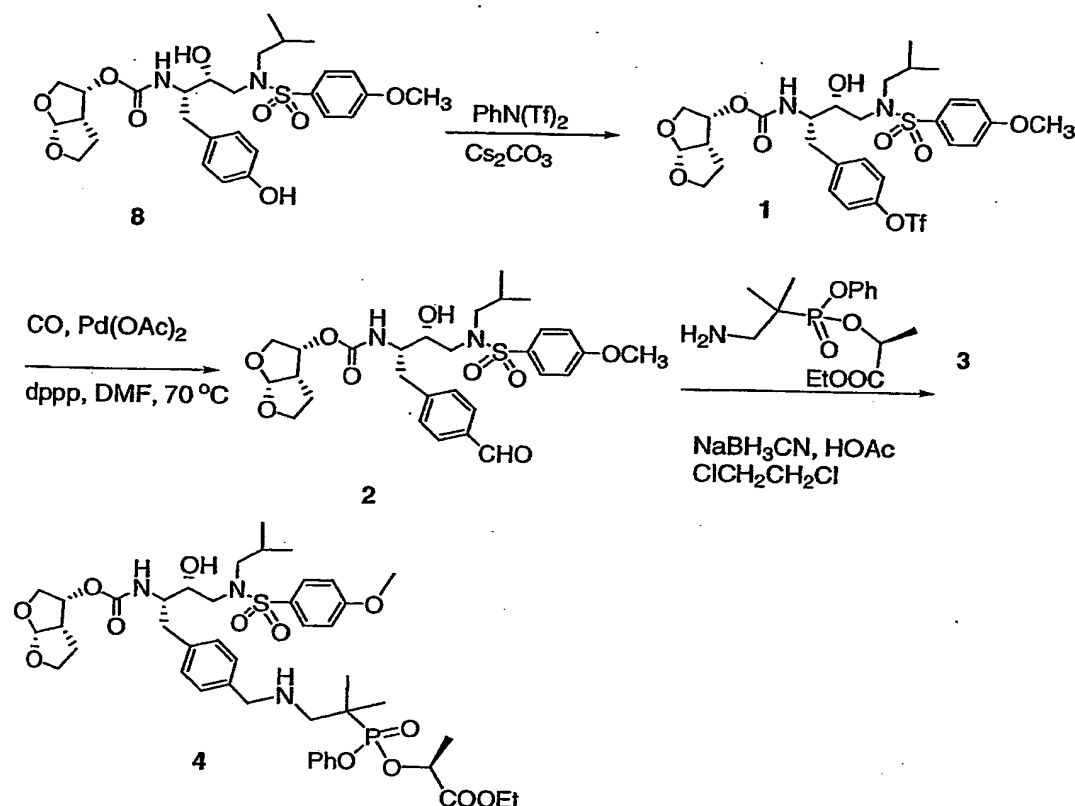
Example 30

Preparation of compound **3** Diethyl (cyano(dimethyl)methyl) phosphonate **5**: A THF
solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmole) was cooled to –10°C,
followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and
iodomethane (17 g, 112 mmol). The resulting solution was stirred at –10°C for 2 hr, then 0°C
for 1 hr, was worked up, and purified to give dimethyl derivative **5** (5 g, 86%).

Dietyl (2-amino-1,1-diemthyl-ethyl)phosphonate **6**: Compound **5** was reduced to amine
derivative **6** by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

A ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of **5** (2.2 g, 10.7 mmol) was
hydrogenated at 1 atmosphere in the presence of PtO_2 (1.25 g) at room temperature
overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to
dryness, to give crude **6** (2.5g, as HCl salt).

2-Amino-1,1-dimethyl-ethyl phosphonic acid **7**: A CH_3CN (30 mL) of crude **6** (2.5 g) was
cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was

stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

5   Lactate phenyl (2-amino-1,1-diemthyl-ethyl)phosphonate **3**: Compound **3** is synthesized according to the procedures described in a previous scheme for the preparation of a lactate phenyl 2-aminoethyl phosponate. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate

10   leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonated derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10% Pd/C and 1 equivalent of TFA affords compound **3** as TFA salt.
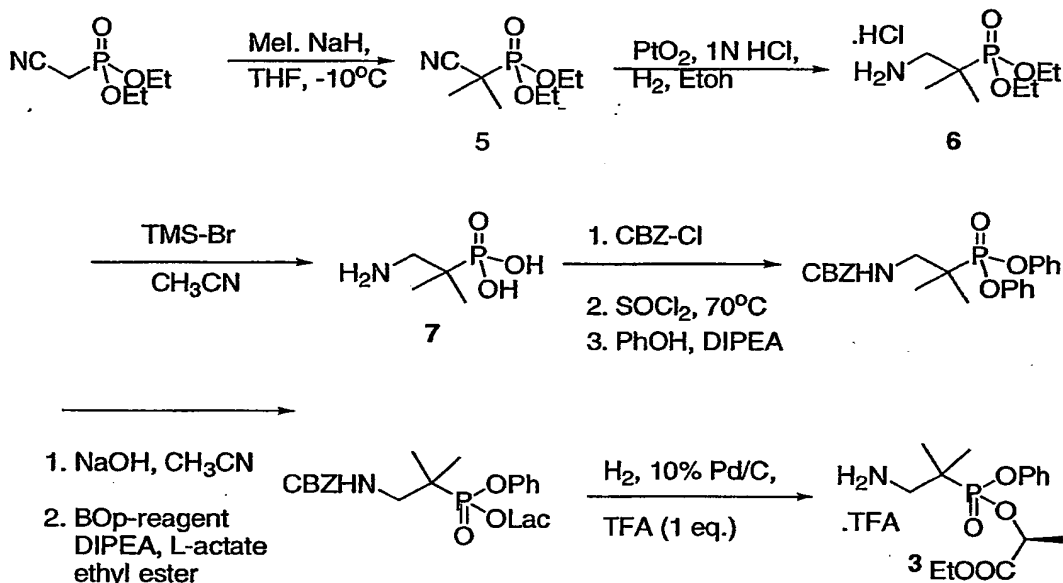
Example Section M

Scheme 1

Scheme 2

5 → [TfO∼P(O)(OBn)₂ / Cs₂CO₃, CH₃CN] → **6**

6 → [(1) TFA, CH₂Cl₂ / (2) Ph-SO₂Cl / TEA, CH₂Cl₂] → **7** GS 191477

→ [Pd / C, H₂ / MeOH, r.t.] → **8** GS 191478

6 → [(1) TFA, CH₂Cl₂ / (2) NC-Ph-SO₂Cl / TEA, CH₂Cl₂] → **9** GS 191717

Scheme 3

6 $\xrightarrow{\begin{array}{c}\text{(1) TFA, CH}_2\text{Cl}_2 \\ \hline \text{(2) F}_3\text{C}-\text{SO}_2\text{Cl} \\ \text{TEA, CH}_2\text{Cl}_2\end{array}}$

10
GS 191479

$\xrightarrow{\begin{array}{c}\text{Pd / C, H}_2 \\ \hline \text{MeOH, r.t.}\end{array}}$

11
GS 191480

6 $\xrightarrow{\begin{array}{c}\text{(1) TFA, CH}_2\text{Cl}_2 \\ \hline \text{(2) F}-\text{SO}_2\text{Cl} \\ \text{TEA, CH}_2\text{Cl}_2\end{array}}$

12
GS 191482

$\xrightarrow{\begin{array}{c}\text{Pd / C, H}_2 \\ \hline \text{MeOH, r.t.}\end{array}}$

13
GS 191483
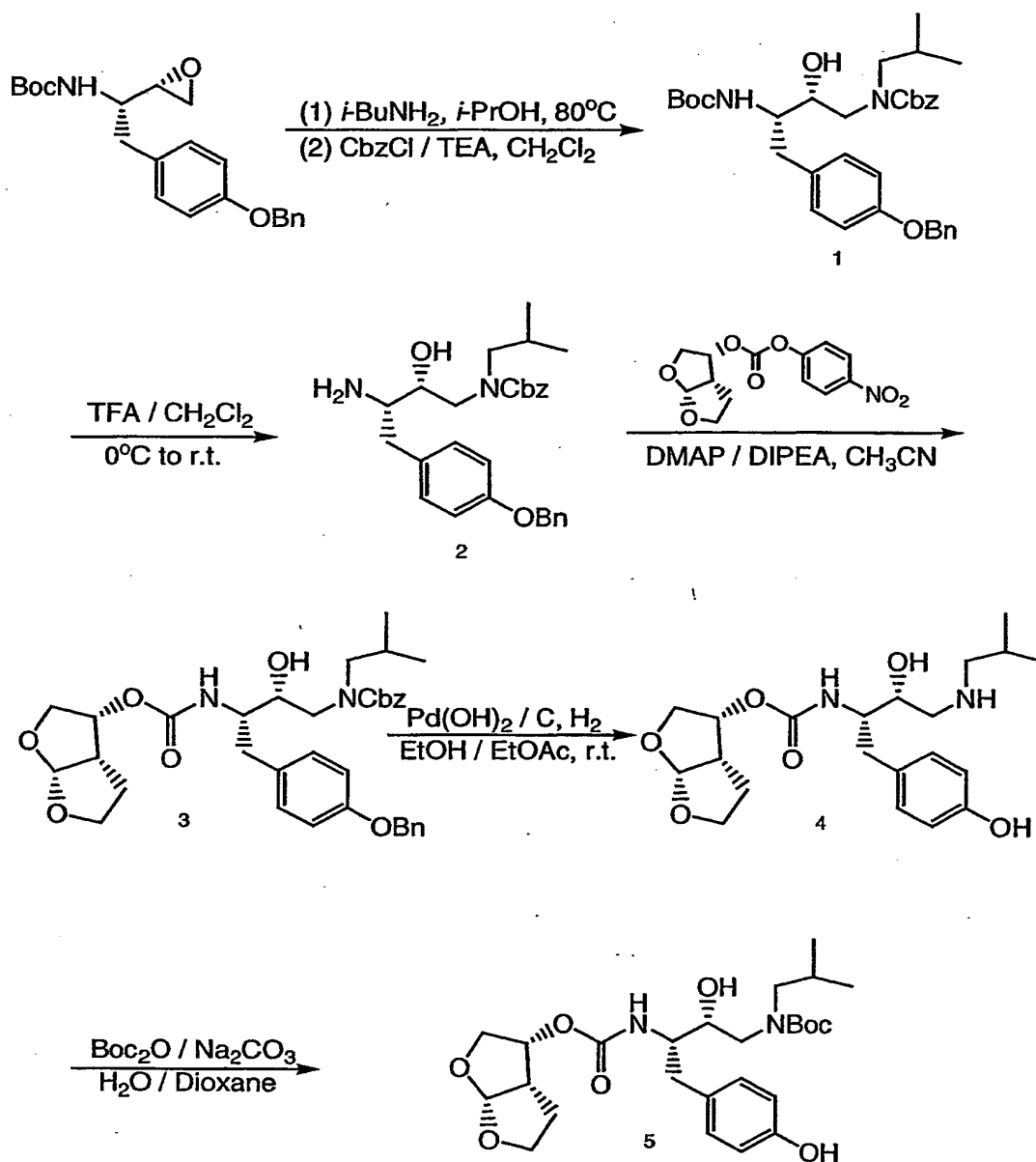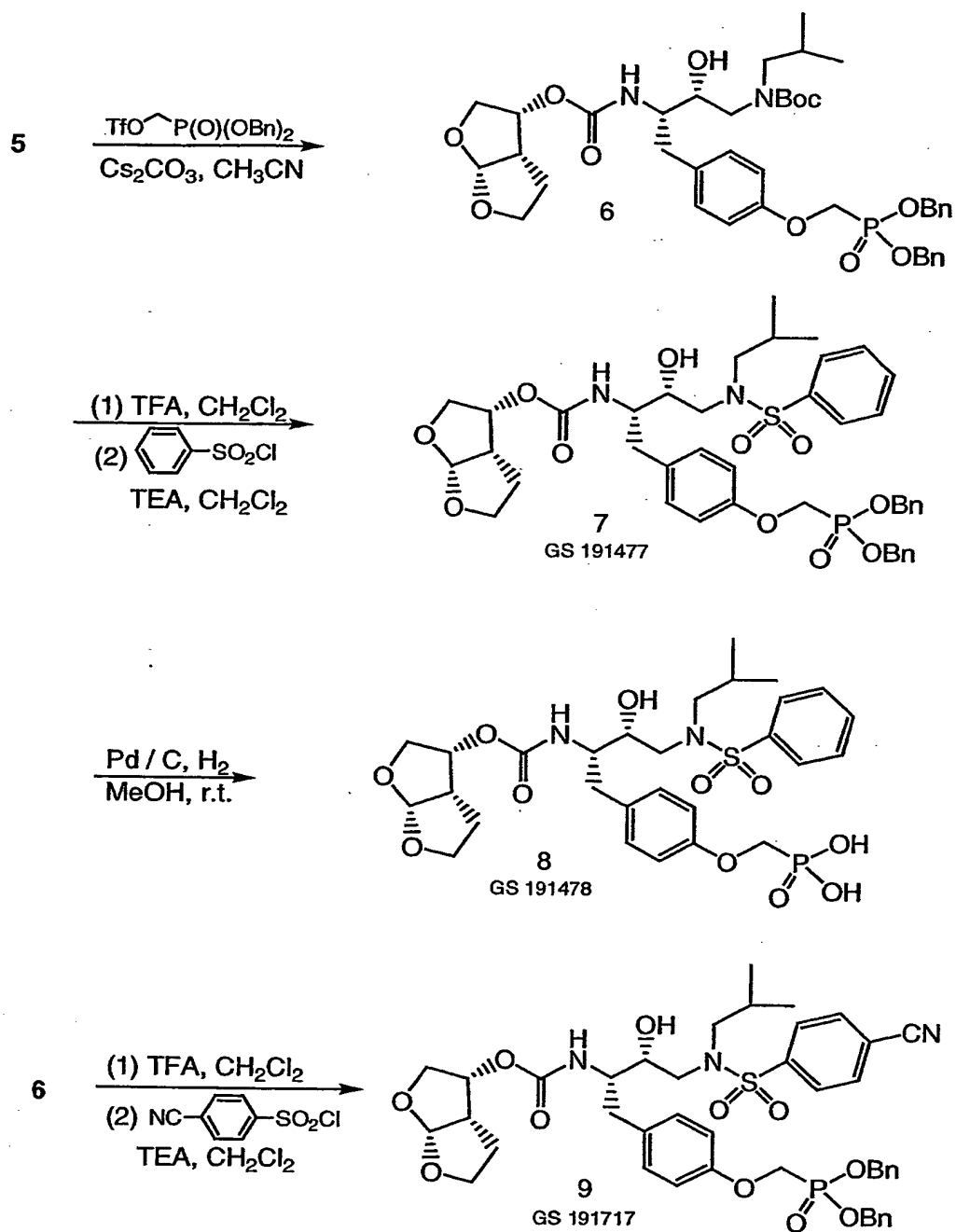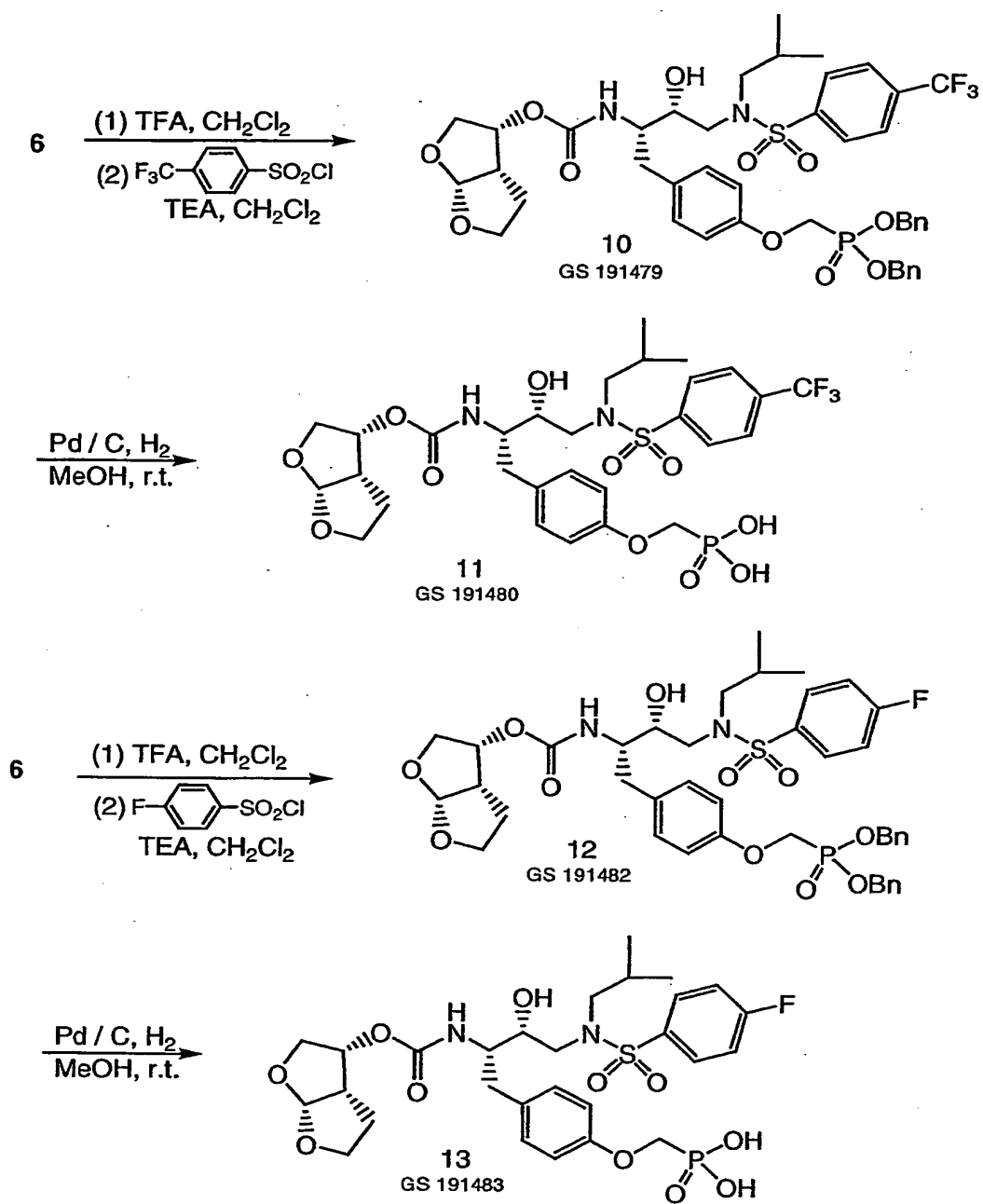
Scheme 4

6 $\xrightarrow[\substack{(2)\ F_3CO-\!\!\langle\rangle\!\!-SO_2Cl\\ \text{TEA, CH}_2\text{Cl}_2}]{(1)\ \text{TFA, CH}_2\text{Cl}_2}$

14
GS 191508

$\xrightarrow[\text{MeOH, r.t.}]{\text{Pd / C, H}_2}$

15
GS 192041

6 $\xrightarrow[\substack{\text{HCl.N}\\ (2)\ -SO_2Cl\\ \text{TEA, CH}_2\text{Cl}_2}]{(1)\ \text{TFA, CH}_2\text{Cl}_2}$

16
GS 273805

$\xrightarrow[\text{MeOH / AcOH}]{\text{Pd / C, H}_2}$

17
GS 273845

Scheme 5

6 $\xrightarrow[\substack{(2)\,ClO_2S-\text{\includegraphics}-CHO\\ \text{TEA, CH}_2\text{Cl}_2}]{(1)\ TFA,\ CH_2Cl_2}$

18
GS 278114

$\xrightarrow[\text{EtOAc, r.t.}]{Pd\,/\,C,\ H_2}$

19

$\xrightarrow[\substack{(2)\ \text{Morpholine, NaBH}_3\text{CN}\\ \text{HOAc, EtOAc}}]{(1)\ BSA,\ CH_3CN,\ reflux}$

20 (GS 278118) R = OH

21 (GS 278117) R = N⏜O
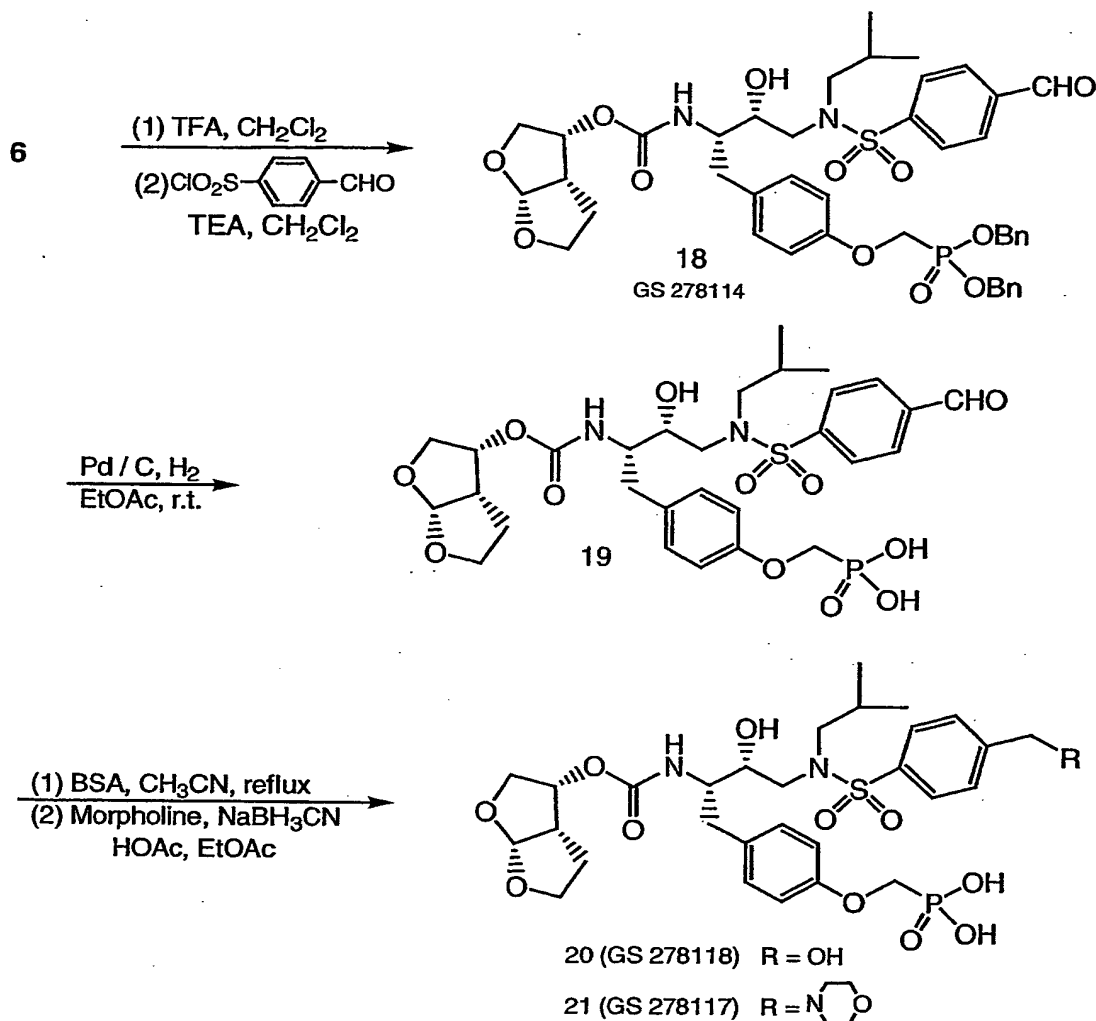
<u>Example 1</u>

5   Cbz Amide 1: To a suspension of epoxide (34 g, 92.03 mmol) in 2-propanol (300 mL) was
added isobutylamine (91.5 mL, 920 mmol) and the solution was refluxed for 1 h. The
solution was evaporated under reduced pressure and the crude solid was dried under vacuum
to give the amine (38.7 g, 95%) which was dissolved in CH_2Cl_2 (300 mL) and cooled to 0°C.
Triethylamine (18.3 mL, 131 mmol) was added followed by the addition of benzyl

10   chloroformate (13.7 mL, 96.14 mmol) and the solution was stirred for 30 min at 0°C, warmed
to room temperature overnight, and evaporated under reduced pressure. The residue was
partitioned between EtOAc and 0.5 M H_3PO_4. The organic phase was washed with saturated
$NaHCO_3$, brine, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The

crude product was purified by column chromatography on silica gel (1/2-EtOAc/hexane) to give the Cbz amide (45.37 g, 90%) as a white solid.

Example 2

5   Amine 2: A solution of Cbz amide 1 (45.37 g, 78.67 mmol) in CH$_2$Cl$_2$ (160 mL) at 0°C was treated with trifluoroacetic acid (80 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), water (2 x), saturated NaCl, dried with
10   Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give the amine (35.62 g, 95%) as a white solid.

Example 3

Carbamate 3: To a solution of amine 2 (20.99 g, 44.03 mmol) in CH$_3$CN (250 mL) at 0°C
15   was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (13.00 g, 44.03 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), N,N-diisopropylethylamine (15.50 mL, 88.06 mmol) and 4-dimethylaminopyridine (1.08 g, 8.81 mmol). The reaction mixture was stirred at 0°C for 30 min and then warmed to room temperature overnight. The reaction solvent was evaporated under reduced pressure and the
20   residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), 5% citric acid (2 x), saturated NaHCO$_3$, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the carbamate (23.00 g, 83%) as a white solid.

25

Example 4

Amine 4: To a solution of 3 (23.00 g, 36.35 mmol) in EtOH (200 mL) and EtOAc (50 mL) was added 20% Pd(OH)$_2$/C (2.30 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of
30   celite. The filtrate was concentrated and dried under vacuum to give the amine (14.00 g, 94%) as a white solid.

Example 5

Phenol 5: To a solution of amine 4 (14.00 g, 34.27 mmol) in H_2O (80 mL) and 1,4-dioxane
(80 mL) at 0°C was added Na_2CO_3 (5.09 g, 47.98 mmol) and di-*tert*-butyl dicarbonate (8.98
g, 41.13 mmol). The reaction mixture was stirred at 0°C for 2 h and then warmed to room
temperature for 30 min. The residue was partitioned between EtOAc and H_2O. The organic
5   layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by
column chromatography on silica gel (3% $MeOH/CH_2Cl_2$) to give the phenol (15.69 g, 90%)
as a white solid.

Example 6

10 Dibenzylphosphonate 6: To a solution of phenol 5 (15.68 g, 30.83 mmol) in CH_3CN (200
mL) was added Cs_2CO_3 (15.07 g, 46.24 mmol) and triflate (17.00 g, 40.08 mmol). The
reaction mixture was stirred at room temperature for 1 h, the salt was filtered off, and the
solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc
and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated
15 under reduced pressure. The crude product was purified by column chromatography on silica
gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (15.37 g, 73%) as a white solid.

Example 7

Sulfonamide 7: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5
20 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30
min at 0°C and then warmed to room temperature for an additional 30 min. The reaction
mixture was diluted with toluene and concentrated under reduced pressure. The residue was
co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the
ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C.
25 Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of
benzenesulfonyl chloride (47 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the
product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was
washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced
pressure. The crude product was purified by column chromatography on silica gel (3% 2-
30 propanol/CH_2Cl_2) to give the sulfonamide 7 (0.12 g, 55%, GS 191477) as a white solid:
^{1}HNMR ($CDCl_3$) δ 7.79 (dd, 2H), 7.61-7.56 (m, 3H), 7.38-7.36 (m, 10H), 7.13 (d, J = 8.4 Hz,
2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.18 (m, 4H), 5.05 (m, 1H), 4.93 (d, J
= 8.7 Hz, 1H), 4.20 (d, J = 10.2 Hz, 2H), 4.0-3.67 (m, 7H), 3.15-2.8 (m, 7H), 1.84 (m, 1H),

1.65-1.59 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.36.

Example 8

Phosphonic Acid 8: To a solution of 7 (70 mg, 0.09 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90% GS 191478) as a white solid: ^{1}HNMR (CD$_3$OD) δ 7.83 (dd, 2H), 7.65-7.56 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 4.96 (m, 1H), 4.15 (d, J = 9.9 Hz, 2H), 3.95-3.68 (m, 6H), 3.44 (dd, 2H), 3.16 (m, 2H), 2.99-2.84 (m, 4H), 2.48 (m, 1H), 2.02 (m, 1H), 1.6 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.45.

Example 9

Sulfonamide 9: A solution of dibenzylphosphonate 6 (0.24 g, 0.31 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (3 mL) and cooled to 0°C. Triethylamine (0.17 mL, 1.20 mmol) was added followed by the treatment of 4-cyanobenzenesulfonyl chloride (61.4 mg, 0.30 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the sulfonamide 9 (0.20 g, 77%, GS 191717) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.36 (m, 10H), 7.11 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.9 (m, 5H), 4.8 (d, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.99 (m 1H), 3.94 (m, 3H), 3.7 (m, 2H), 3.48 (broad, s, 1H), 3.18-2.78 (m, 7H), 1.87 (m, 1H), 1.66-1.47 (m, 2H), 0.91 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.3..

Example 10

Sulfonamide 10: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-trifluoromethyl benzenesulfonyl chloride (72 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the sulfonamide (0.13 g, 50%, GS 191479) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.20-4.89 (m, 6H), 4.20 (d, J = 9.9 Hz, 2H), 3.95 (m, 1H), 3.86 (m, 3H), 3.71 (m, 2H), 3.19-2.78 (m, 7H), 1.86 (m, 1H), 1.65 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.3.

Example 11

Phosphonic Acid 11: To a solution of 10 (70 mg, 0.079 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 191480) as a white solid: ^{1}H NMR (CD$_3$OD) δ 8.03 (dd, 2H), 7.90 (dd, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.7 Hz, 1H), 4.94 (m, 1H), 4.15 (d, J = 10.2 Hz, 2H), 3.94-3.72 (m, 6H), 3.48 (m, 1H), 3.2-3.1 (m, 3H), 3.0-2.9 (m, 2H), 2.47 (m, 1H), 2.06 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.5.

Example 12

Sulfonamide 12: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction
5 mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (57 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C
10 and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 55%, GS 191482) as a white solid: ^1H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.38 (m, 10H), 7.24 (m, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.82 (d,
15 J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.0 (m, 1H), 4.90 (d, 1H), 4.20 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.73 (m, 2H), 3.6 (broad, s, 1H), 3.13 (m, 1H), 3.03-2.79 (m, 6H), 1.86 (m, 1H), 1.66-1.58 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.
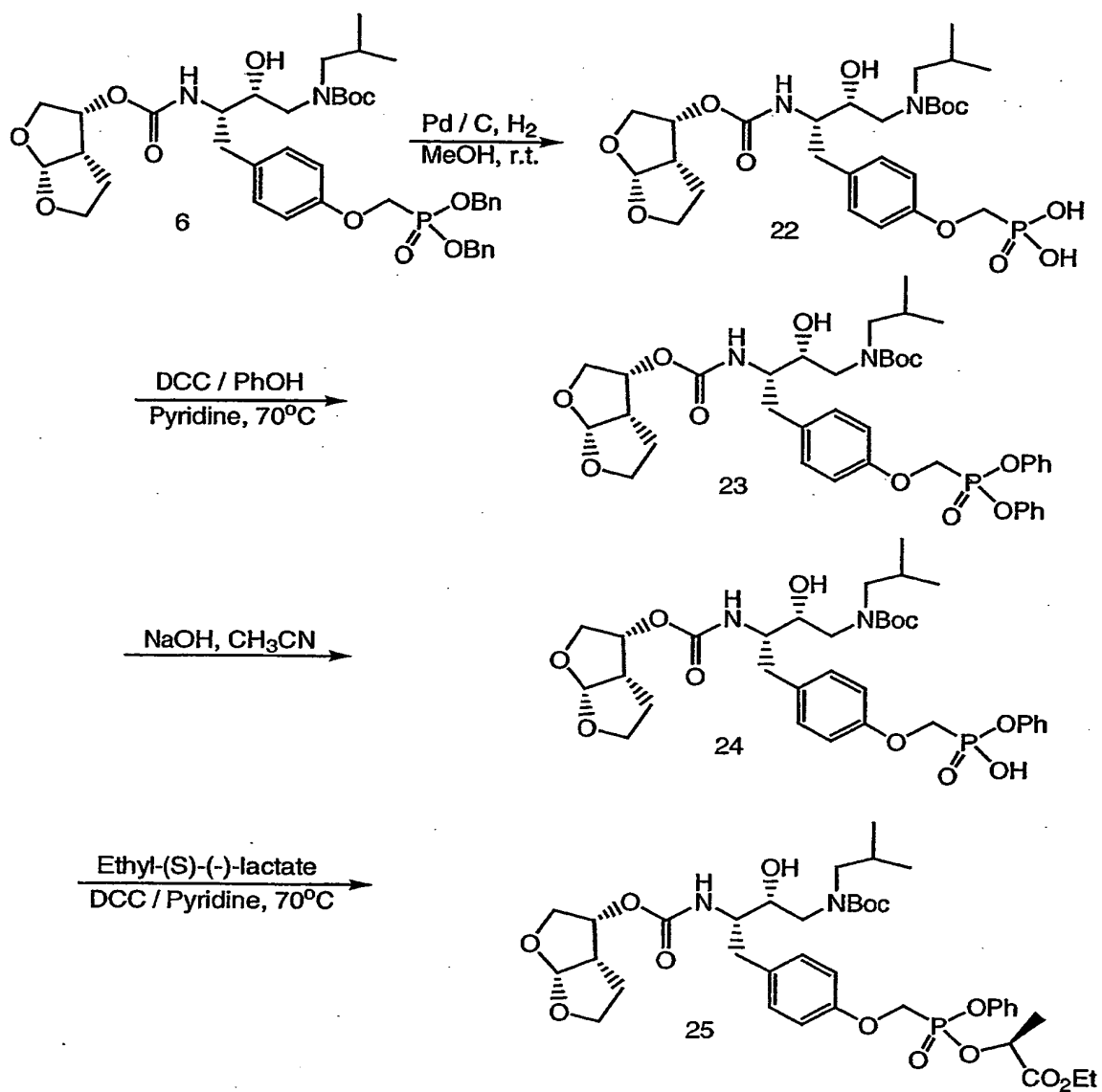

20 Example 13

Phosphonic Acid 13: To a solution of 12 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90%,
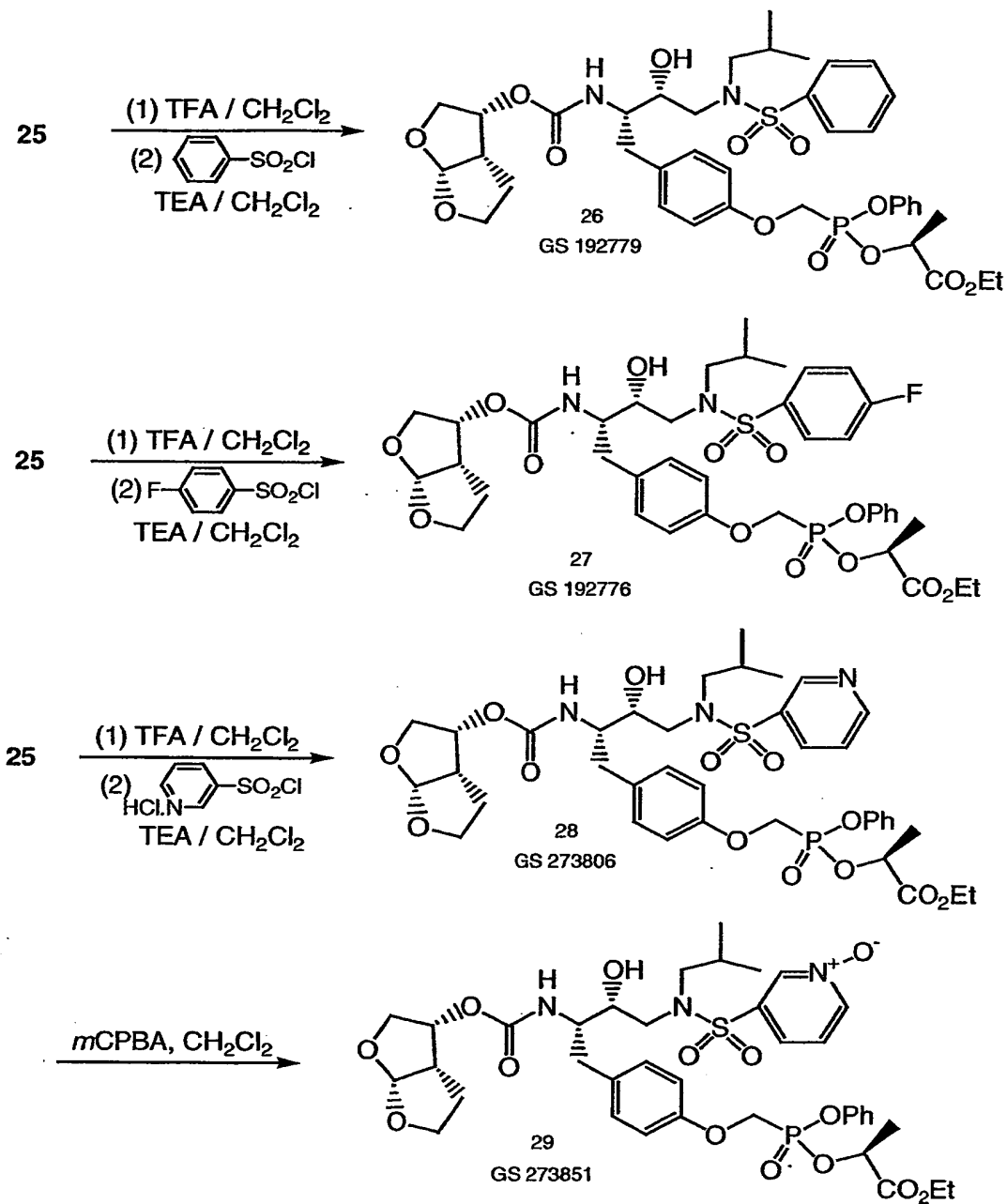25 GS 191483) as a white solid: ^1H NMR (CD_3OD) δ 7.89 (m, 2H), 7.32 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.1 Hz, 2H), 5.59 (d, J = 5.1 Hz, 1H), 4.94 (m, 1H), 4.16 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85-3.7 (m, 5H), 3.43 (dd, 1H), 3.15-2.87 (m, 5H), 2.48 (m, 1H), 2.03 (m, 1H), 1.59-1.36 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.5.

30

Example 14

Sulfonamide 14: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was

5   co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of 4-trifluoromethoxybenzenesulfonyl chloride (69 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The

10   organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.17 g, 70%, GS 191508) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.84 (d, J = 9 Hz, 2H), 7.36 (m, 12H), 7.12 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.16 (m, 4H), 5.03 (m, 1H), 4.89 (d, 1H),

15   4.2 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.59 (broad, s, 1H), 3.18 (m, 1H), 3.1-3.0 (m, 3H), 2.96-2.78 (m, 3H), 1.86 (m, 1H), 1.66-1.5 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{1}P NMR (CDCl$_3$) δ 20.3.

Example 15

20   Phosphonic Acid 15: To a solution of 14 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 192041) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.95 (dd, 2H), 7.49 (dd, 2H), 7.17 (dd,

25   2H), 6.92 (dd, 2H), 5.58 (d, J = 5.4 Hz, 1H), 4.89 (m, 1H), 4.17 (d, J = 9 Hz, 2H), 3.9 (m, 1H), 3.82-3.7 (m, 5H), 3.44 (m, 1H), 3.19-2.9 (m, 5H), 2.48 (m, 1H), 2.0 (m, 1H), 1.6 (m, 1H), 1.35 (m, 1H), 0.93 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.4.

30   ## Example 16

Sulfonamide 16: A solution of dibenzylphosphonate 6 (0.59 g, 0.76 mmol) in CH_2Cl_2 (2.0 mL) at 0°C was treated with trifluoroacetic acid (1.0 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction

mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.53 mL, 3.80 mmol) was added followed by the treatment of hydrogen

5   chloride salt of 3-pyridinylsulfonyl chloride (0.17 g, 0.80 mmol, prepared according to Karaman, R. et al. J. Am. Chem. Soc. 1992, 114, 4889). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was

10 purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.50 g, 80%, GS 273805) as a white solid: ^1H NMR ($CDCl_3$) δ 9.0 (d, J = 1.5 Hz, 1H), 8.8 (dd, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.48 (m, 1H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.18 (m, 4H), 5.06 (m, 1H), 4.93 (d, 1H), 4.21 (d, J = 8.4 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.74 (m, 2H), 3.2 (m, 1H), 3.1-

15 2.83 (m, 5H), 2.76 (m, 1H), 1.88 (m, 1H), 1.62 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 17

Phosphonic Acid 17: To a solution of 16 (40 mg, 0.049 mmol) in MeOH (3 mL) and AcOH

20 (1 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (28 mg, 90%, GS 273845) as a white solid: ^1H NMR (CD_3OD) δ 8.98 (s, 1H), 8.77 (broad, s, 1H), 8.25 (dd, 1H), 7.6 (m, 1H), 7.15 (m, 2H), 6.90 (m, 2H), 5.6 (d, J = 5.4 Hz, 1H), 4.98 (m,

25 1H), 4.15 (d, 2H), 3.97-3.7 (m, 6H), 3.45-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.9 (m, 6H).

Example 18

Sulfonamide 18: A solution of dibenzylphosphonate 6 (0.15 g, 0.19 mmol) in CH_2Cl_2 (0.60

30 mL) at 0°C was treated with trifluoroacetic acid (0.30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the

ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.11 mL, 0.76 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (43 mg, 0.21 mmol). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between

5   CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 80%, GS 278114) as a white solid: ^1H NMR (CDCl$_3$) δ 10.1 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.35 (m, 10H), 7.13 (m, J = 8.1 Hz, 2H),

10   6.82 (d, J = 8.1 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.06 (m, 1H), 4.93 (m, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.18-2.87 (m, 5H), 2.78 (m, 1H), 1.86 (m, 1H), 1.67-1.58 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.3.

15   <u>Example 19</u>

Phosphonic Acid 19: To a solution of 18 (0.12 g, 0.15 mmol) in EtOAc (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (93 mg, 95%) as a

20   white solid.

   <u>Example 20</u>

Phosphonic Acids 20 and 21: Compound 19 (93 mg, 0.14 mmol) was dissolved in CH_3CN (2 mL). N,O-Bis(trimethylsilyl)acetamide (BSA, 0.28 g, 1.4 mmol) was added. The reaction

25   mixture was heated to reflux for 1 h, cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a semi-solid which was dissolved in EtOAc (2 mL). Morpholine (60 μL, 0.9 mmol), AcOH (32 μL, 0.56 mmol), and NaBH$_3$CN (17 mg, 0.28 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O, stirred for

30   2 h, filtered, and concentrated. The crude product was purified by HPLC to give the phosphonic acid 20 (10 mg, GS 278118) as a white solid: ^1H NMR (CD$_3$OD) δ 7.80 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 5.59

(d, J = 5.1 Hz, 1H), 5.06 (m, 1H), 4.7 (s, 2H), 4.15 (d, J = 10.2 Hz, 2H), 3.92 (m, 1H), 3.82-
3.7 (m, 5H), 3.43 (dd, 1H), 3.11-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H),
0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.3.   Phosphonic
acid 21 (15 mg, GS 278117) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.8-7.7 (m, 4H), 7.20 (d, J

5   = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 5.1 Hz, 1H), 5.00 (m, 1H), 4.42 (s, 2H),
4.20 (dd, 2H), 3.98-3.68 (m, 9H), 3.3-2.92 (m, 11H), 2.6 (m, 1H), 2.0 (m, 1H), 1.6 (m, 2H),
0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 16.2.

Scheme 6

Scheme 7

25 →(1) TFA / CH₂Cl₂ ; (2) Ph-SO₂Cl ; TEA / CH₂Cl₂→ **26** GS 192779

25 →(1) TFA / CH₂Cl₂ ; (2) F-Ph-SO₂Cl ; TEA / CH₂Cl₂→ **27** GS 192776

25 →(1) TFA / CH₂Cl₂ ; (2) HCl·N-pyridine-SO₂Cl ; TEA / CH₂Cl₂→ **28** GS 273806

→ *m*CPBA, CH₂Cl₂ → **29** GS 273851

Scheme 8

28 $\xrightarrow[\text{CHCl}_3]{\text{MeOTf}}$

30
GS 273813

16 $\xrightarrow{\text{MeOTf, CHCl}_3}$

31
GS 273812

16 $\xrightarrow[\text{CH}_2\text{Cl}_2]{m\text{CPBA}}$

32
GS 277774

$\xrightarrow[\text{MeOH, r.t.}]{\text{Pd / C, H}_2}$

33
GS 277775

Scheme 9

25    $\xrightarrow[\begin{array}{c}(2)\ ClO_2S-\!\!\!\begin{array}{c}\end{array}\!\!\!-CHO\\ TEA\ /\ CH_2Cl_2\end{array}]{(1)\ TFA\ /\ CH_2Cl_2}$

34
GS 278052

$\xrightarrow[\text{HOAc, EtOAc, r.t.}]{\text{Morpholine, NaBH}_3\text{CN}}$

35
GS 278115

25    $\xrightarrow[\begin{array}{c}(2)\ TEA\ /\ CH_2Cl_2\\ BnO-\!\!\!\begin{array}{c}\end{array}\!\!\!-SO_2Cl\\ \mathbf{36}\end{array}]{(1)\ TFA\ /\ CH_2Cl_2}$

37

$\xrightarrow[\text{EtOH, r.t.}]{\text{Pd / C, H}_2}$

38
GS 273838

-1372-

Scheme 10

25 $\xrightarrow[\text{TEA / CH}_2\text{Cl}_2]{\begin{array}{c}\text{(1) TFA / CH}_2\text{Cl}_2\\ \text{(2) }\underset{\textbf{39}}{\text{CbzN}\diagdown\text{N}\diagdown\text{SO}_2\text{Cl}}\end{array}}$

40

$\xrightarrow[\text{MeOH / EtOAc}]{\text{Pd / C, H}_2\text{, TFA}}$

41

$\xrightarrow[\text{NaBH}_3\text{CN, EtOAc}]{\text{HCHO / HOAc}}$

42
GS 277937

Scheme 11

43

HO⟶CH₃
      |
      O 44
      ‖
      O⟶OBn

DCC / Pyridine, 70 °C

45

Pd(OH)₂ / C, H₂
EtOAc, r.t.

46
GS 278809

Example 21

Phosphonic Acid 22: To a solution of dibenzylphosphonate 6 (5.00 g, 6.39 mmol) in EtOH (100 mL) was added 10% Pd/C (1.4 g). The suspension was stirred under H₂ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (3.66 g, 95%) as a white solid.

Example 22

Diphenylphosphonate 23: A solution of 22 (3.65 g, 6.06 mmol) and phenol (5.70 g, 60.6 mmol) in pyridine (30 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (5.00 g, 24.24 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off.

5 The filtrate was concentrated and dissolved in CH₃CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the diphenylphosphonate (2.74 g, 60%) as a white solid.

10

Example 23

Monophosphonic Acid 24: To a solution of 23 (2.74 g, 3.63 mmol) in CH₃CN (40 mL) at 0°C was added 1 N NaOH (9.07 mL, 9.07 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was

15 stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.34 g, 95%) as a white solid.

Example 24

20 Monophospholactate 25: A solution of 24 (2.00 g, 2.95 mmol) and ethyl-(S)-(-)-lactate (1.34 mL, 11.80 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.43 g, 11.80 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned

25 between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H₂O, saturated NaCl, dried with Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the monophospholactate (1.38 g, 60%) as a white solid.

30 Example 25

Monophospholactate 26: A solution of 25 (0.37 g, 0.48 mmol) in CH₂Cl₂ (0.80 mL) at 0°C was treated with trifluoroacetic acid (0.40 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was

diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH₂Cl₂ (3 mL) and cooled to 0°C. Triethylamine (0.27 mL, 1.92 mmol) was added followed by the treatment of

5   benzenesulfonyl chloride (84 mg, 0.48 mmol). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The product was partitioned between CH₂Cl₂ and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the

10   monophospholactate (0.33 g, 85%, GS 192779, 1:1 diastereomeric mixture) as a white solid: ¹H NMR (CDCl₃) δ 7.78 (dd, 2H), 7.59 (m, 3H), 7.38-7.18 (m, 7H), 6.93 (dd, 2H), 5.66 (m, 1H), 5.18-4.93 (m, 3H), 4.56-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.17 (m, 1H), 3.02-2.8 (m, 6H), 1.84 (m, 1H), 1.82-1.5 (m, 5H), 1.27 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ³¹P NMR (CDCl₃) δ 17.4, 15.3.

15

Example 26

Monophospholactate 27: A solution of 25 (0.50 g, 0.64 mmol) in CH₂Cl₂ (1.0 mL) at 0°C was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted

20   with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH₂Cl₂ (4 mL) and cooled to 0°C. Triethylamine (0.36 mL, 2.56 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (0.13 g, 0.64 mmol). The solution was stirred for 30 min at 0°C and then warmed to room

25   temperature for 30 min. The product was partitioned between CH₂Cl₂ and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the monophospholactate (0.44 g, 81%, GS 192776, 3/2 diastereomeric mixture) as a white solid: ¹H NMR (CDCl₃) δ 7.80 (m, 2H), 7.38-7.15 (m,

30   9H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-4.9 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.6 (broad, s, 1H), 3.17 (m, 1H), 3.02-2.75 (m, 6H), 1.85 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ³¹P NMR (CDCl₃) δ 17.3, 15.2.

Example 27

Monophospholactate 28: A solution of 25 (0.50 g, 0.64 mmol) in CH$_2$Cl$_2$ (1.0 mL) at 0°C

was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and

then warmed to room temperature for an additional 30 min. The reaction mixture was diluted

5   with toluene and concentrated under reduced pressure. The residue was co-evaporated with

toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt

which was dissolved in CH$_2$Cl$_2$ (3 mL) and cooled to 0°C. Triethylamine (0.45 mL, 3.20

mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl

chloride (0.14 g, 0.65 mmol). The solution was stirred for 30 min at 0°C and then warmed to

10   room temperature for 30 min. The product was partitioned between CH$_2$Cl$_2$ and H$_2$O. The

organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated

under reduced pressure. The crude product was purified by column chromatography on silica

gel (4% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.41 g, 79%, GS 273806, 1:1

diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 9.0 (s, 1H), 8.83 (dd, 1H), 8.06

15   (d, J = 7.8 Hz, 1H), 7.5 (m, 1H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.18-4.95

(m, 3H), 4.6-4.41 (m, 2H), 4.2 (m, 2H), 4.0 (m, 1H), 3.95-3.76 (m, 6H), 3.23-2.8 (m, 7H),

1.88 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz,

3H); ^{31}P NMR (CDCl$_3$) δ 17.3, 15.3.

20   Example 28

Monophospholactate 29: A solution of compound 28 (0.82 g, 1.00 mmol) in CH$_2$Cl$_2$ (8 mL)

at 0°C was treated with mCPBA (1.25 eq). The solution was stirred for 1 h at 0°C and then

warmed to room temperature for an additional 6 h. The reaction mixture was partitioned

between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic phase was washed with saturated

25   NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude

product was purified by column chromatography on silica gel (10% 2-propanol/CH$_2$Cl$_2$) to

give the monophospholactate (0.59 g, 70%, GS 273851, 1:1 diastereomeric mixture) as a

white solid: ^{1}H NMR (CDCl$_3$) δ 8.63 (dd, 1H), 8.3 (dd, 1H), 7.57 (m, 1H), 7.44 (m, 1H),

7.38-7.13 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.05 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m,

30   2H), 4.0-3.73 (m, 6H), 3.2 (m, 2H), 3.0 (m, 4H), 2.77 (m, 1H), 1.92 (m, 1H), 1.7-1.49 (m,

5H), 1.26 (m, 3H), 0.91 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.3, 15.3.

Example 29

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Monophospholactate 30: A solution of compound 28 (71 mg, 0.087 mmol) in CHCl$_3$ (1 mL) was treated with MeOTf (18 mg, 0.11 mmol). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x), CHCl$_3$ (2 x) and dried under vacuum to give the monophospholactate (81 mg, 95%, GS 273813, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 9.0 (dd, 1H), 8.76 (m, 2H), 8.1 (m, 1H), 7.35-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.25-5.0 (m, 3H), 4.6-4.41 (m, 5H), 4.2 (m, 2H), 3.92-3.72 (m, 6H), 3.28 (m, 2H), 3.04-2.85 (m, 3H), 2.62 (m, 1H), 1.97 (m, 1H), 1.62-1.5 (m, 5H), 1.25 (m, 3H), 0.97 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.4, 15.4.

Example 30

Dibenzylphosphonate 31: A solution of compound 16 (0.15 g, 0.18 mmol) in CHCl$_3$ (2 mL) was treated with MeOTf (37 mg, 0.23 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x), CHCl$_3$ (2 x) and dried under vacuum to give the dibenzylphosphonate (0.17 g, 95%, GS 273812) as a white solid: ^{1}H NMR (CDCl$_3$) δ 9.0 (dd, 1H), 8.73 (m, 2H), 8.09 (m, 1H), 7.35 (m, 10H), 7.09 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.1 Hz, 2H), 5.61 (d, J = 4.2 Hz, 1H), 5.2-4.96 (m, 6H), 4.54 (s, 3H), 4.2 (dd, 2H), 3.92-3.69 (m, 6H), 3.3 (m, 2H), 3.04-2.6 (m, 5H), 1.97 (m, 1H), 1.6 (m, 2H), 0.98 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 20.4.

Example 31

Dibenzylphosphonate 32: A solution of compound 16 (0.15 g, 0.18 mmol) in CH$_2$Cl$_2$ (3 mL) at 0°C was treated with mCPBA (1.25 eq). The solution was stirred for 1 h at 0°C and then warmed to room temperature overnight. The reaction mixture was partitioned between 10% 2-propanol/CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH$_2$Cl$_2$) to give the dibenzylphosphonate (0.11 g, 70%, **GS 277774**) as a white solid: ^{1}H NMR (CDCl$_3$) δ 8.64 (m, 1H), 8.27 (d, J = 6.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.36 (m, 11H), 7.10 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.22-5.02 (m, 6H), 4.21 (dd, 2H), 3.99-3.65 (m, 6H), 3.2 (m, 2H), 3.03-2.73 (m, 5H), 1.90 (m, 1H), 1.66-1.56 (m, 2H), 0.91 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 20.3.

Example 32

Phosphonic Acid 33: To a solution of dibenzylphosphonate 32 (0.1 g, 0.12 mmol) in MeOH
(4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H₂ atmosphere
(balloon) at room temperature for 1 h. The reaction mixture was filtered through a plug of

5   celite. The filtrate was concentrated and purified by HPLC to give the phosphonic acid (17
mg, **GS 277775**) as a white solid: ^{1}H NMR (CD₃OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H),
7.92 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.14 (m, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.58 (d, J = 5.4
Hz, 1H), 5.00 (m, 1H), 4.08 (d, J = 9.9 Hz, 2H), 3.93-3.69 (m, 6H), 3.4-2.9 (m, 7H), 2.5 (m,
1H), 2.04 (m, 1H), 1.6-1.35 (m, 2H), 0.92 (m, 6H); ^{31}P NMR (CD₃OD) δ 15.8.

10

Example 33

Monophospholactate 34: A solution of 25 (2.50 g, 3.21 mmol) in CH₂Cl₂ (5.0 mL) at 0°C
was treated with trifluoroacetic acid (2.5 mL). The solution was stirred for 30 min at 0°C and
then warmed to room temperature for an additional 30 min. The reaction mixture was diluted

15   with toluene and concentrated under reduced pressure. The residue was co-evaporated with
toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt
which was dissolved in CH₂Cl₂ (30 mL) and cooled to 0°C. Triethylamine (1.79 mL, 12.84
mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (0.72 g,
3.53 mmol) and the solution was stirred at 0°C for 1 h. The product was partitioned between

20   CH₂Cl₂ and 5% HCl. The organic phase was washed with H₂O, saturated NaCl, dried with
Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by
column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the
monophospholactate (2.11 g, 77%, GS 278052, 1:1 diastereomeric mixture) as a white solid:
^{1}H NMR (CDCl₃) δ 10.12 (s, 1H), 8.05 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 7.5 Hz, 2H), 7.38-

25   7.15 (m, 7H), 6.94 (m, 2H), 5.67 (m, 1H), 5.18-4.91 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H),
4.0-3.69 (m, 6H), 3.57 (broad, s, 1H), 3.19-2.8 (m, 7H), 1.87 (m, 1H), 1.69-1.48 (m, 5H),
1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl₃) δ 17.3,
15.2.

30   Example 34

Monophospholactate 35: A solution of 34 (0.60 g, 0.71 mmol) and morpholine (0.31 mL,
3.54 mmol) in EtOAc (8 mL) was treated with HOAc (0.16 mL, 2.83 mmol) and NaBH₃CN
(89 mg, 1.42 mmol). The reaction mixture was stirred at room temperature for 4 h. The

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product was partitioned between EtOAc and H$_2$O. The organic phase was washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.46 g, 70%, GS 278115, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.74

5   (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.0 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.57 (m, 12H), 3.2-2.78 (m, 7H), 2.46 (broad, s, 4H), 1.87 (m, 1H), 1.64-1.5 (m, 5H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.3, 15.3.

10   Example 35

Monophospholactate 37: A solution of 25 (0.50 g, 0.64 mmol) in CH$_2$Cl$_2$ (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with

15   toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (3 mL) and cooled to 0°C. Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (0.18 g, 0.64 mmol, prepared according to Toja, E. et al. Eur. J. Med. Chem. 1991, 26, 403). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The

20   product was partitioned between CH$_2$Cl$_2$ and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.51 g, 85%) as a white solid.

25   Example 36

Monophospholactate 38: To a solution of 37 (0.48 g, 0.52 mmol) in EtOH (15 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on

30   silica gel (5% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.38 g, 88%, GS 273838, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 8.86 (dd, 1H), 7.42-7.25 (m, 9H), 6.91 (m, 4H), 5.73 (d, J = 5.1 Hz, 1H), 5.42 (m, 1H), 5.18 (m, 2H), 4.76-4.31 (m, 2H), 4.22 (m, 2H), 4.12-3.75 (m, 6H), 3.63 (broad, s, 1H), 3.13 (m, 3H), 2.87 (m, 1H), 2.63

(m, 1H), 2.4 (m, 1H), 2.05 (m, 2H), 1.9 (m, 1H), 1.8(m, 1H), 1.6 (m, 3H), 1.25 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.1, 15.7.

Example 37

Monophospholactate 40: A solution of 25 (0.75 g, 0.96 mmol) in CH$_2$Cl$_2$ (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (4 mL) and cooled to 0°C. Triethylamine (0.67 mL, 4.80 mmol) was added followed by the treatment of 4-(4'-benzyloxycarbonyl piperazinyl)benzenesulfonyl chloride (0.48 g, 1.22 mmol, prepared according to Toja, E. et al. Arzneim. Forsch. 1994, 44, 501). The solution was stirred at 0°C for 1 h and then warmed to room temperature for 30 min. The product was partitioned between 10% 2-propanol/CH$_2$Cl$_2$ and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.63 g, 60%) as a white solid.

Example 38

Monophospholactate 41: To a solution of 40 (0.62 g, 0.60 mmol) in MeOH (8 mL) and EtOAc (2 mL) was added 10% Pd/C (0.20 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was treated with 1.2 equivalent of TFA, co-evaporated with CHCl$_3$ and dried under vacuum to give the monophospholactate (0.55 g, 90%) as a white solid.

Example 39

Monophospholactate 42: A solution of 41 (0.54 g, 0.53 mmol) and formaldehyde (0.16 mL, 5.30 mmol) in EtOAc (10 mL) was treated with HOAc (0.30 mL, 5.30 mmol) and NaBH$_3$CN (0.33 g, 5.30 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between EtOAc and H$_2$O. The organic phase was washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column

chromatography on silica gel (6% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (97.2

mg, 20%, GS 277937, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.64

(d, J = 9.0 Hz, 2H), 7.38-7.17 (m, 7H), 6.95-6.88 (m, 4H), 5.67 (m, 1H), 5.2-4.96 (m, 2H),

4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.64 (m, 8H), 3.49-3.37 (m, 4H), 3.05-2.78 (m, 12H),

5 1.88-1.62 (m, 3H), 1.58 (m, 3H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz,

3H); ^{31}P NMR (CDCl$_3$) δ 17.3, 15.3.

Example 40

Monophospholactate 45: A solution of 43 (0.12 g, 0.16 mmol) and lactate 44 (0.22 g, 1.02

10 mmol) in pyridine (1 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.17 g, 0.83

mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room

temperature. The solvent was removed under reduced pressure. The residue was suspended

in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between

EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H$_2$O, saturated NaCl,

15 dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column

chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (45

mg, 26%) as a white solid.

Example 41

20 Alcohol 46: To a solution of 45 (40 mg, 0.042 mmol) in EtOAc (2 mL) was added 20%

Pd(OH)$_2$/C (10 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room

temperature for 3 h. The reaction mixture was filtered through a plug of celite. The filtrate

was concentrated and the product was dried under vacuum to give the alcohol (33 mg, 90%,

GS 278809, 3/2 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7

25 Hz, 2H), 7.39-7.15 (m, 7H), 7.02-6.88 (m, 4H), 5.66 (d, J = 4.5 Hz, 1H), 5.13-5.02 (m, 2H),

4.54-4.10 (m, 4H), 4.00-3.69 (m, 11H), 3.14 (m, 1H), 3.02-2.77 (m, 6H), 1.85-1.6 (m, 6H),

0.94 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4, 15.9.

Scheme 12

$$\xrightarrow[\text{reflux, 2 h}]{\text{DABCO, toluene}}$$

$$\xrightarrow[\text{DMF, r.t.}]{\substack{\text{Benzyl-(S)-(-)-lactate} \\ \text{PyBop, DIPEA, DMAP}}}$$

(1) TFA, CH$_2$Cl$_2$
(2) ⟨C$_6$H$_5$⟩–SO$_2$Cl
TEA, CH$_2$Cl$_2$

Scheme 13

$$\underset{\text{EtOH / EtOAc}}{\xrightarrow{\text{Pd / C, H}_2}}$$

49

50
GS 224342

48   $\xrightarrow[\substack{(2)\text{F}-\langle\text{aryl}\rangle-\text{SO}_2\text{Cl} \\ \text{TEA, CH}_2\text{Cl}_2}]{(1)\ \text{TFA, CH}_2\text{Cl}_2}$

51

$$\underset{\text{EtOH / EtOAc}}{\xrightarrow{\text{Pd / C, H}_2}}$$

52
GS 224343

Scheme 14

48 → **(1)** TFA, CH₂Cl₂
(2) TEA, CH₂Cl₂

53

Pd / C, H₂
EtOH, r.t.

54
GS 273834

48 → **(1)** TFA / CH₂Cl₂
(2) TEA / CH₂Cl₂
BnO—⟨⟩—SO₂Cl

55

Pd / C, H₂
EtOH, r.t.

56
GS 273847

Scheme 15

29 — Esterase, PBS buffer / CH₃CN / DMSO, 40°C →

57
GS 277777

35 — Esterase, PBS buffer / CH₃CN / DMSO, 40°C →

58
GS 278116

34 — NaBH₄, -15°C / THF / H₂O (9/1) →

59
GS 278503

Esterase, PBS buffer / CH₃CN / DMSO, 40°C →

60
GS 278764

Example 42

Monobenzylphosphonate 47: A solution of 6 (2.00 g, 2.55 mmol) and DABCO (0.29 g, 2.55 mmol) in toluene (10 mL) was heated to reflux for 2 h. The solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H₂O, saturated NaCl, dried with Na₂SO₄, filtered, and concentrated.

The crude product was dried under vacuum to give the monobenzylphosphonate (1.68 g, 95%) as a white solid.

Example 43

5   Monophospholactate 48: To a solution of 47 (2.5 g, 3.61 mmol) and benzyl-(S)-(-)-lactate (0.87 mL, 5.42 mmol) in DMF (12 mL) was added PyBop (2.82 g, 5.42 mmol) and *N,N*-diisopropylethylamine (2.51 mL, 14.44 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H_2O, saturated NaCl, dried with Na_2SO_4, filtered,

10   and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (1.58 g, 51%) as a white solid.

Example 44

Monophospholactate 49: A solution of 48 (0.30 g, 0.35 mmol) in CH_2Cl_2 (0.6 mL) at 0°C

15   was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.20 mL, 1.40

20   mmol) was added followed by the treatment of benzenesulfonyl chloride (62 mg, 0.35 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the

25   monophospholactate (0.17 g, 53%) as a white solid.

Example 45

Metabolite X 50: To a solution of 49 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere

30   (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with $CHCl_3$ and dried under vacuum to give the metabolite X (61 mg, 95%, GS 224342) as a white solid: ^{1}H NMR (CD_3OD) δ 7.83 (d, J = 6.9 Hz, 2H), 7.65-7.58 (m, 3H), 7.18 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.59

(d, J = 4.8 Hz, 1H), 5.0 (m, 1H), 4.27 (d, J = 10.2 Hz, 2H), 3.95-3.68 (m, 6H), 3.45 (dd, 1H),

3.18-2.84 (m, 6H), 2.50 (m, 1H), 2.02 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H),

0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD), δ 18.0.

5   Example 46

Monophospholactate 51: A solution of 48 (0.28 g, 0.33 mmol) in CH$_2$Cl$_2$ (0.6 mL) at 0°C

was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and

then warmed to room temperature for an additional 30 min. The reaction mixture was diluted

with toluene and concentrated under reduced pressure. The residue was co-evaporated with

10   toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt

which was dissolved in CH$_2$Cl$_2$ (2 mL) and cooled to 0°C. Triethylamine (0.18 mL, 1.32

mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (64 mg,

0.33 mmol). The solution was stirred at 0°C for 30 min and then warmed to room

temperature for 30 min. The product was partitioned between CH$_2$Cl$_2$ and 0.1 N HCl. The

15   organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and

concentrated. The crude product was purified by column chromatography on silica gel (3%

2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.16 g, 52%) as a white solid.

Example 47

20   Metabolite X 52: To a solution of 51 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2

mL) was added 10% Pd/C (20 mg). The suspension was stirred under H$_2$ atmosphere

(balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of

celite. The filtrate was concentrated, co-evaporated with CHCl$_3$ and dried under vacuum to

give the metabolite X (61 mg, 95%, GS 224343) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.9

25   (dd, 2H), 7.32 (m, 2H), 7.18 (dd, 2H), 6.90 (dd, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H),

4.28 (d, J = 10.2 Hz, 2H), 3.95-3.72 (m, 6H), 3.44 (dd, 1H), 3.15-2.85 (m, 6H), 2.5 (m, 1H),

2.02 (m, 1H), 1.55-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). ^{31}P NMR
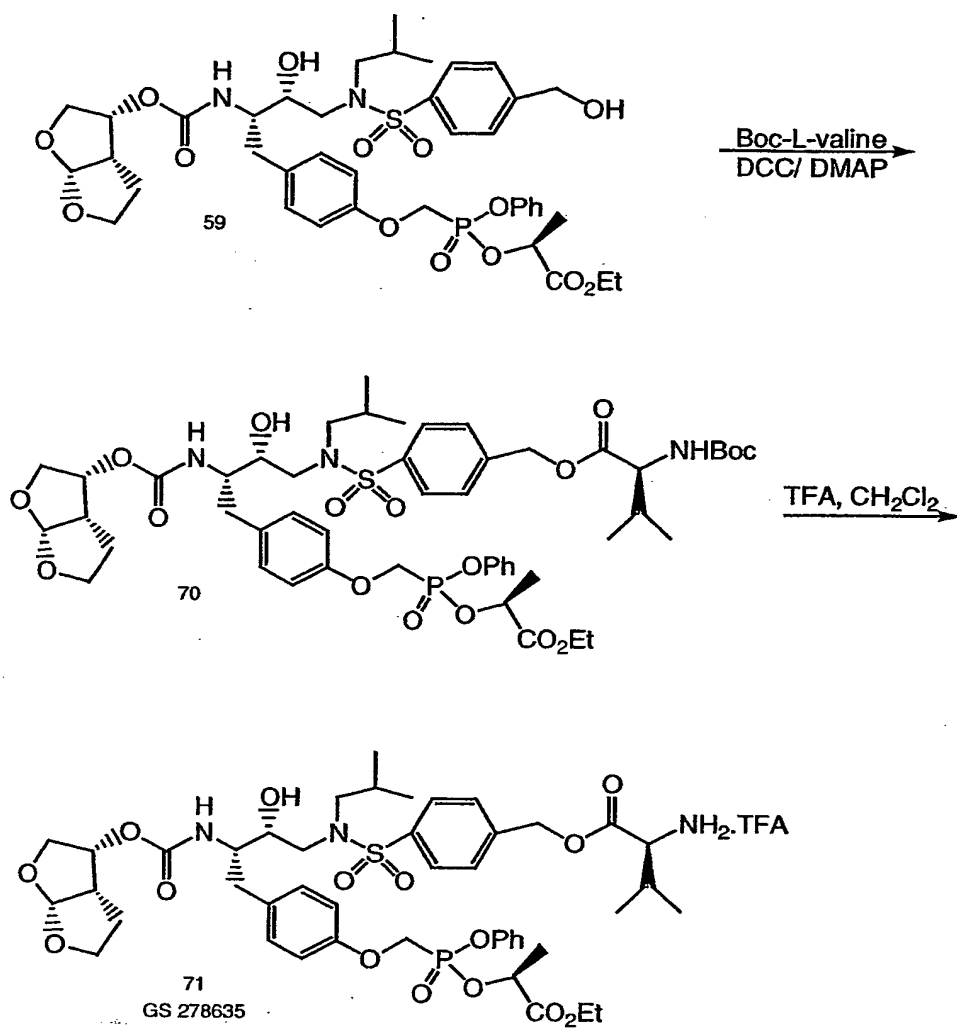
(CD$_3$OD) δ 18.2.

30   Example 48

Monophospholactate 53: A solution of 48 (0.20 g, 0.24 mmol) in CH$_2$Cl$_2$ (0.6 mL) at 0°C

was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and

then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.20

5   mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinysulfonyl chloride (50 mg, 0.24 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and H_2O. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4%

10   2-propanol/CH_2Cl_2) to give the monophospholactate (0.11 g, 53%) as a white solid.

Example 49

Metabolite X 54: To a solution of 53 (70 mg, 0.09 mmol) in EtOH (5 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room

15   temperature for 5 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with $CHCl_3$ and dried under vacuum to give the metabolite X (53 mg, 95%, GS 273834) as a white solid: ^{1}H NMR (CD$_3$OD) δ 8.99 (s, 1H), 8.79 (d, J = 4.2 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 7.7 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.28 (d, J = 9.9 Hz, 2H), 3.97-3.70 (m, 6H), 3.44

20   (dd, 1H), 3.17-2.85 (m, 6H), 2.5 (m, 1H), 2.03 (m, 1H), 1.65-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). ^{31}P NMR (CD$_3$OD) δ 17.8.

Example 50

Monophospholactate 55: A solution of 48 (0.15 g, 0.18 mmol) in CH_2Cl_2 (1 mL) at 0°C was

25   treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.12 mL, 0.88

30   mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (50 mg, 0.18 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and

concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (0.11 g, 63%) as a white solid.

Example 51

5   Metabolite X 56: To a solution of 55 (70 mg, 0.07 mmol) in EtOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with CHCl$_3$ and dried under vacuum to give the metabolite X (46 mg, 90%, GS 273847) as a white solid: ^{1}H NMR (CD$_3$OD), δ 7.91 (s, 1H), 7.65 (d, J =

10   8.4 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (m, 4H), 5.59 (d, J = 5.1 Hz, 1H), 5.0 (m, 1H), 4.27 (d, J = 10.2 Hz, 2H), 3.97-3.74 (m, 6H), 3.4 (dd, 1H), 3.17-2.8 (m, 6H), 2.5 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.9.

15   Example 52

Metabolite X 57: To a suspension of 29 (40 mg, 0.05 mmol) in CH$_3$CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (200 µL). The suspension was heated to 40°C for 48 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 57%,

20   GS 277777) as a white solid: ^{1}H NMR (CD$_3$OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.23 (d, J = 10.5 Hz, 2H), 3.97-3.68 (m, 6H), 3.45 (dd, 1H), 3.15-2.87 (m, 6H), 2.46 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.2.

25

Example 53

Metabolite X 58: To a suspension of 35 (60 mg, 0.07 mmol) in CH$_3$CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (400 µL). The suspension was heated to 40°C for 3 days. The reaction mixture was concentrated, suspended in MeOH and filtered.

30   The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 38%, GS 278116) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.74 (d, J = 6.9 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.0 (m,

2H), 4.41 (m, 2H), 4.22 (m, 2H), 3.97-3.65 (m, 12H), 3.15-2.9 (m, 8H), 2.75 (m, 1H), 2.0 (m, 1H), 1.8 (m, 2H), 1.53 (d, J = 6.9 Hz, 3H), 0.88 (m, 6H).

Example 54

Monophospholactate 59: A solution of 34 (2.10 g, 2.48 mmol) in THF (72 mL) and H_2O (8 mL) at -15°C was treated with $NaBH_4$ (0.24 g, 6.20 mmol). The reaction mixture was stirred for 10 min at -15°C. The reaction was quenched with 5% aqueous $NaHSO_3$ and extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give monophospholactate (1.89 g, 90%, GS 278053, 1:1 diastereomeric mixture) as a white solid: ^1H NMR ($CDCl_3$) δ 7.64 (m, 2H), 7.51(m, 2H), 7.38-7.19 (m, 7H), 6.92 (m, 2H), 5.69 (d, J = 4.8 Hz, 1H), 5.15 (m, 2H), 4.76 (s, 2H), 4.54 (d, J = 10.5 Hz, 1H), 4.44 (m, 1H), 4.2 (m, 2H), 4.04-3.68 (m, 6H), 3.06-2.62 (m, 7H), 1.8 (m, 3H), 1.62-1.5 (dd, 3H), 1.25 (m, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4, 15.4.

Example 55

Metabolite X 60: To a suspension of 59 (70 mg, 0.08 mmol) in CH_3CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (600 μL). The suspension was heated to 40°C for 36 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (22 mg, 36%, GS 278764) as a white solid: ^1H NMR (CD_3OD) δ 7.78 (dd, 2H), 7.54 (dd, 2H), 7.15 (m, 2H), 6.9 (m, 2H), 5.57 (d, 1H), 5.0 (m, 2H), 4.65 (m, 4H), 4.2 (m, 2H), 3.9-3.53 (m, 6H), 3.06-2.82 (m, 6H), 2.5 (m, 1H), 2.0 (m, 2H), 1.62-1.35 (m, 3H), 0.94 (m, 6H).

Scheme 16

(1) H$_2$NCH$_2$—⟨ ⟩—P(O)(OH)$_2$
         62
BSA / CH$_3$CN, reflux

(2) NaBH$_3$CN, HOAc, EtOAc
(3) 2% HF, CH$_3$CN

63
GS 277929

HCHO, NaBH$_3$CN
HOAC, EtOAc, r.t.

64
GS 277935

Scheme 17

Reagents and conditions over the first arrow:

(1) H_2N—CH_2CH_2—$P(O)(OH)_2$
BSA / CH_3CN

(2) $NaBH_3CN$, HOAc
EtOAc, r.t.

Compound **65**

Compound **66**

Reagents and conditions over the second arrow:

(1) BSA / CH_3CN, reflux

(2) $NaBH_3CN$, HCHO
HOAc, EtOAc, r.t.

Compound **67**
GS 277957

Scheme 18

68

NaOH, CH₃CN, r.t.

69
GS 273842
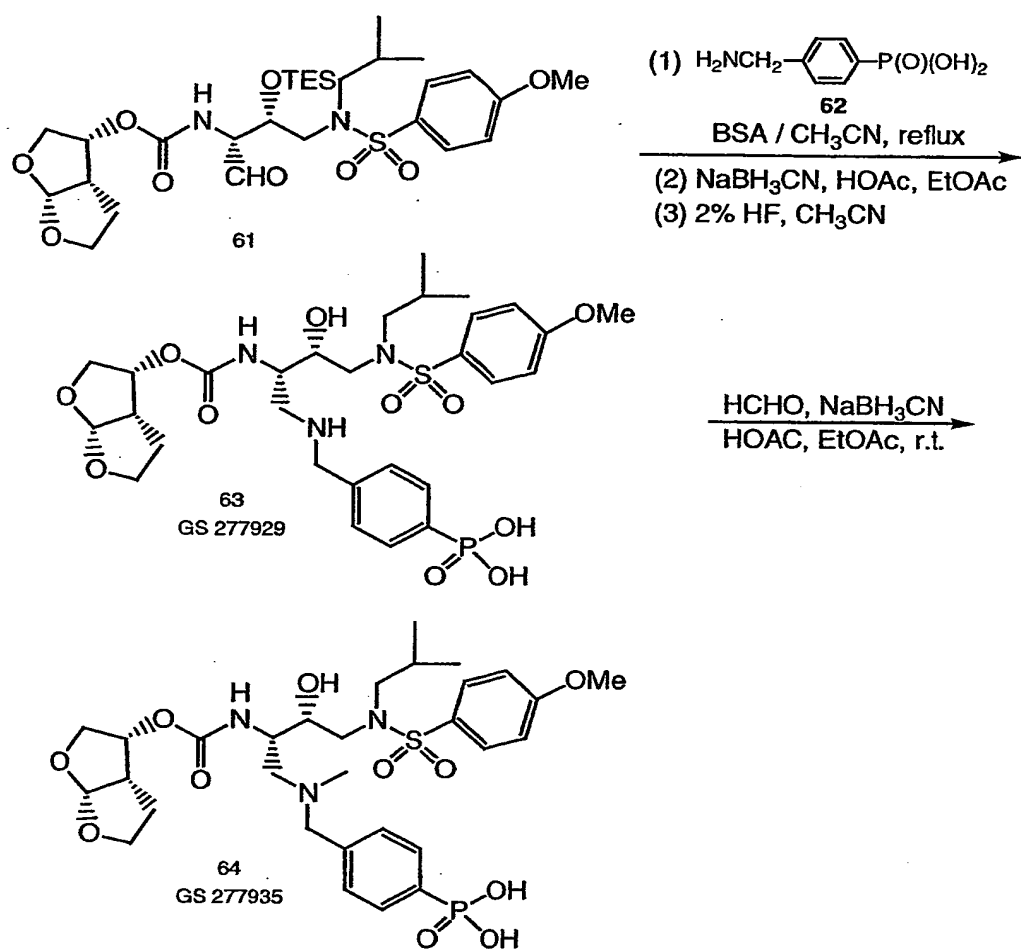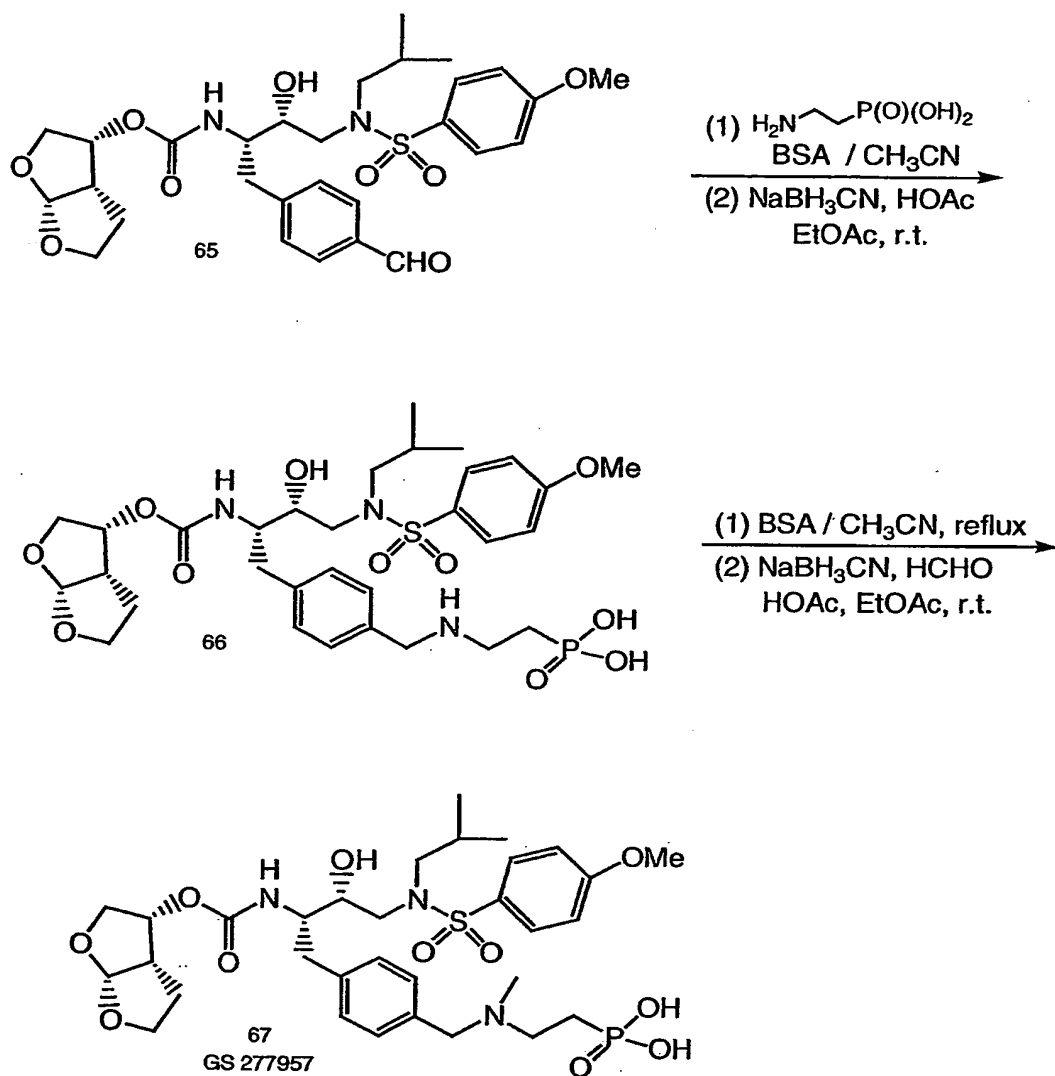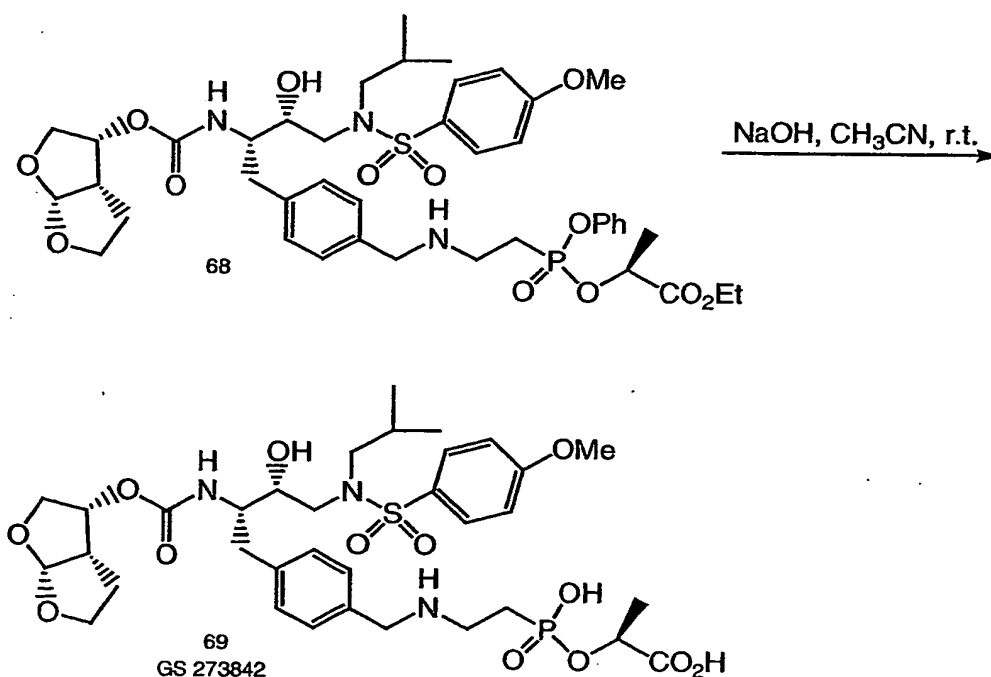
<u>Example 56</u>

Phosphonic Acid 63: Compound 62 (0.30 g, 1.12 mmol) was dissolved in CH₃CN (5 mL).
N,O-Bis(trimethylsilyl)acetamide (BSA, 2.2 mL, 8.96 mmol) was added. The reaction
mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The
residue was co-evaporated with toluene and chloroform and dried under vacuum to give a
thick oil which was dissolved in EtOAc (4 mL) and cooled to 0°C. Aldehyde 61 (0.20 g, 0.33
mmol), AcOH (0.18 mL, 3.30 mmol), and NaBH₃CN (0.20 g, 3.30 mmol) were added. The
reaction mixture was warmed to room temperature and stirred overnight. The reaction was
quenched with H₂O, stirred for 30 min, filtered, and concentrated. The crude product was
dissolved in CH₃CN (13 mL) and 48% aqueous HF (0.5 mL) was added. The reaction
mixture was stirred at room temperature for 2 h and concentrated. The crude product was
purified by HPLC to give the phosphonic acid (70 mg, 32%, GS 277929) as a white solid: ¹H
NMR (CD₃OD) δ 7.92 (dd, 2H), 7.73 (d, J = 8.7 Hz, 2H), 7.63 (dd, 2H), 7.12 (d, J = 8.7 Hz,
2H), 5.68 (d, J = 5.1 Hz, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 1H), 3.5
(m, 1H), 3.37 (m, 1H), 3.23-3.0 (m, 3H), 2.88-2.7 (m, 2H), 2.2 (m, 1H), 1.8 (m, 2H), 0.92 (d,
J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ³¹P NMR (CD₃OD) δ 14.5.

Example 57

Phosphonic Acid 64: A solution of 63 (50 mg, 0.07 mmol) and formaldehyde (60 mg, 0.70

mmol) in EtOAc (2 mL) was treated with HOAc (43 μL, 0.70 mmol) and NaBH₃CN (47 mg,

5   0.7 mmol). The reaction mixture was stirred at room temperature for 26 h. The reaction was

quenched with H₂O, stirred for 20 min, and concentrated. The crude product was purified by

HPLC to give the phosphonic acid (15 mg, 29%, GS 277935) as a white solid: ^{1}H NMR

(CD₃OD) δ 7.93 (m, 2H), 7.75 (m, 2H), 7.62 (m, 2H), 7.11 (m, 2H), 5.66 (m, 1H), 5.13 (m,

1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 2H), 3.09-2.71 (m, 6H), 2.2 (m, 1H), 1.9 (m,

10   5H), 0.92 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD₃OD) δ 14.0.

Example 58

Phosphonic Acid 66: 2-Aminoethylphosphonic acid (2.60 g, 21.66 mmol) was dissolved in

CH₃CN (40 mL). N,O-Bis(trimethylsilyl)acetamide (BSA, 40 mL) was added. The reaction

15   mixture was heated to reflux for 2 h and cooled to room temperature and concentrated. The

residue was co-evaporated with toluene and chloroform and dried under vacuum to give a

thick oil which was dissolved in EtOAc (40 mL). Aldehyde 65 (1.33 g, 2.25 mmol), AcOH

(1.30 mL, 22.5 mmol) and NaBH₃CN (1.42 g, 22.5 mmol) were added. The reaction mixture

was stirred at room temperature overnight. The reaction was quenched with H₂O, stirred for

20   1 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered. The crude

product was purified by HPLC to give the phosphonic acid (1.00 g, 63%) as a white solid.

Example 59

Phosphonic Acid 67: Phosphonic acid 66 (0.13 g, 0.19 mmol) was dissolved in CH₃CN (4

25   mL). N,O-Bis(trimethylsilyl)acetamide (BSA, 0.45 mL, 1.90 mmol) was added. The

reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated.

The residue was co-evaporated with toluene and chloroform and dried under vacuum to give

a thick oil which was dissolved in EtOAc (3 mL). Formaldehyde (0.15 mL, 1.90 mmol),

AcOH (0.11 mL, 1.90 mmol) and NaBH₃CN (63 mg, 1.90 mmol) were added. The reaction

30   mixture was stirred at room temperature overnight. The reaction was quenched with H₂O,

stirred for 6 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered.

The crude product was purified by HPLC to give the phosphonic acid (40 mg, 30%, GS

277957) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.78 (d, J = 8.4 Hz, 2H), 7.4 (m, 4H), 7.09 (d, J = 8.4 Hz, 2H), 5.6 (d, J = 5.1 Hz, 1H), 4.33 (m, 2H), 3.95-3.65 (m, 9H), 3.5-3.05 (m, 6H), 2.91-2.6 (m, 7H), 2.0 (m, 3H), 1.5 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 19.7.

5

Example 60

Metabolite X 69: Monophospholactate 68 (1.4 g, 1.60 mmol) was dissolved in CH$_3$CN (20 mL) and H$_2$O (20 mL). 1.0 N NaOH (3.20 mL, 3.20 mmol) was added. The reaction mixture

10 was stirred at room temperature for 1.5 h and cooled to 0°C. The reaction mixture was acidified to pH = 1-2 with 2 N HCl (1.6 mL, 3.20 mmoL). The solvent was evaporated under reduced pressure. The crude product was purified by HPLC to give the metabolite X (0.60 g, 49%, GS 273842) as a white solid: ^{1}H NMR (DMSO-d$_6$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.33 (m, 4H), 7.09 (d, J = 9.0 Hz, 2H), 5.52 (d, J = 5.7 Hz, 1H), 5.1 (broad, s, 1H), 4.85 (m, 1H), 4.63

15 (m, 1H), 4.13 (m, 2H), 3.8 (m, 5H), 3.6 (m, 4H), 3.36 (m, 1H), 3.03 (m, 4H), 2.79 (m, 3H), 2.5 (m, 1H), 2.0 (m, 3H), 1.5-1.3 (m, 5H), 0.85 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H); ^{31}P NMR (DMSO-d$_6$) δ 21.9.

Scheme 19

Boc-L-valine / DCC/ DMAP →

TFA, CH₂Cl₂ →

Scheme 20

72

Boc-L-valine
DCC/ DMAP

73

TFA, CH₂Cl₂

74
GS 278785

Scheme 21

75

(1) BSA, CH$_3$CN, reflux
(2) CbzCl, Pyridine
    CH$_2$Cl$_2$, 0°C to r.t.

76

(1) Dibenzyldiisopropyl-
    phosphoramidite
    1H-tetrazole, r.t.
(2) mCPBA, CH$_2$Cl$_2$

77

(1) Pd / C, H$_2$
    EtOH / EtOAc
(2) NaHCO$_3$, H$_2$O

78
GS 277962
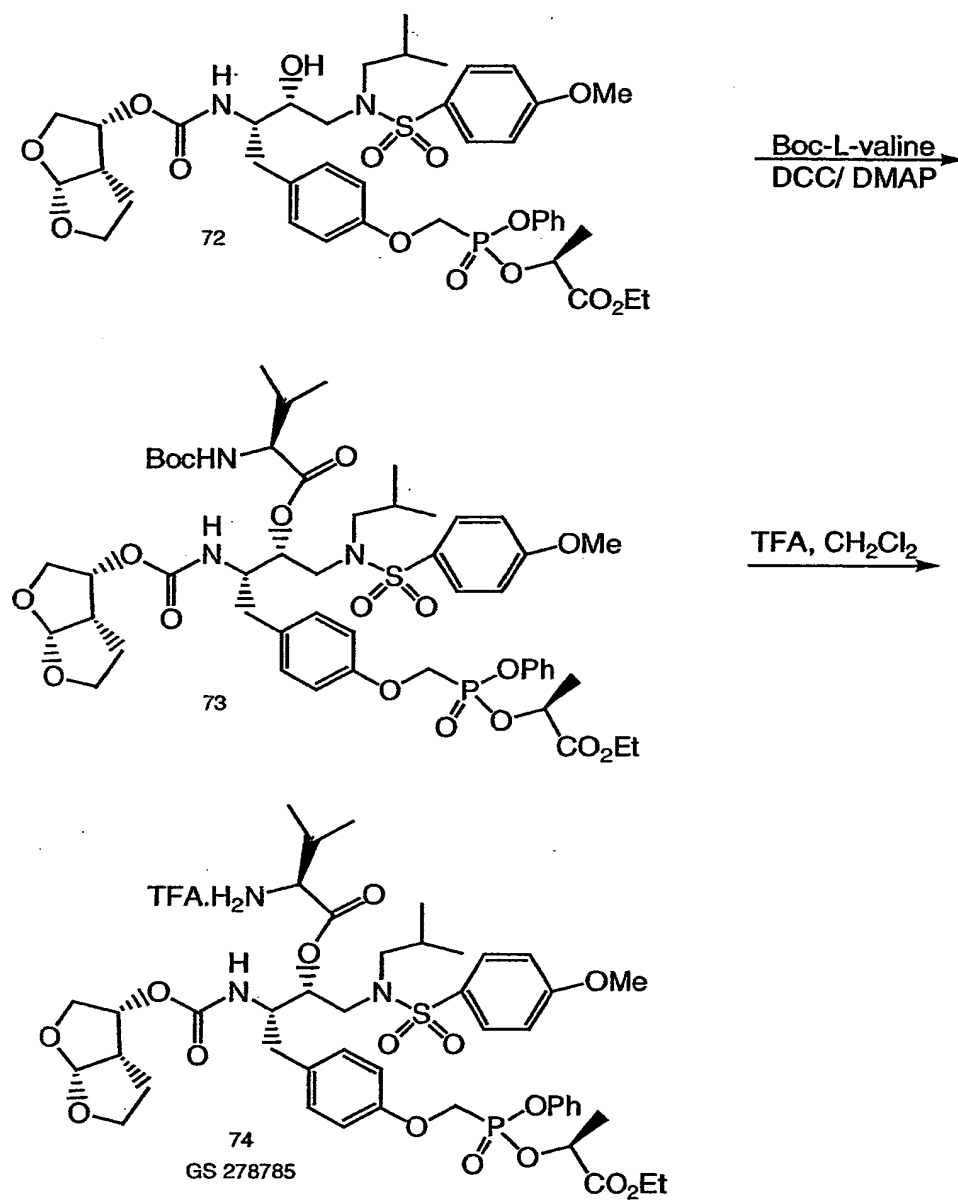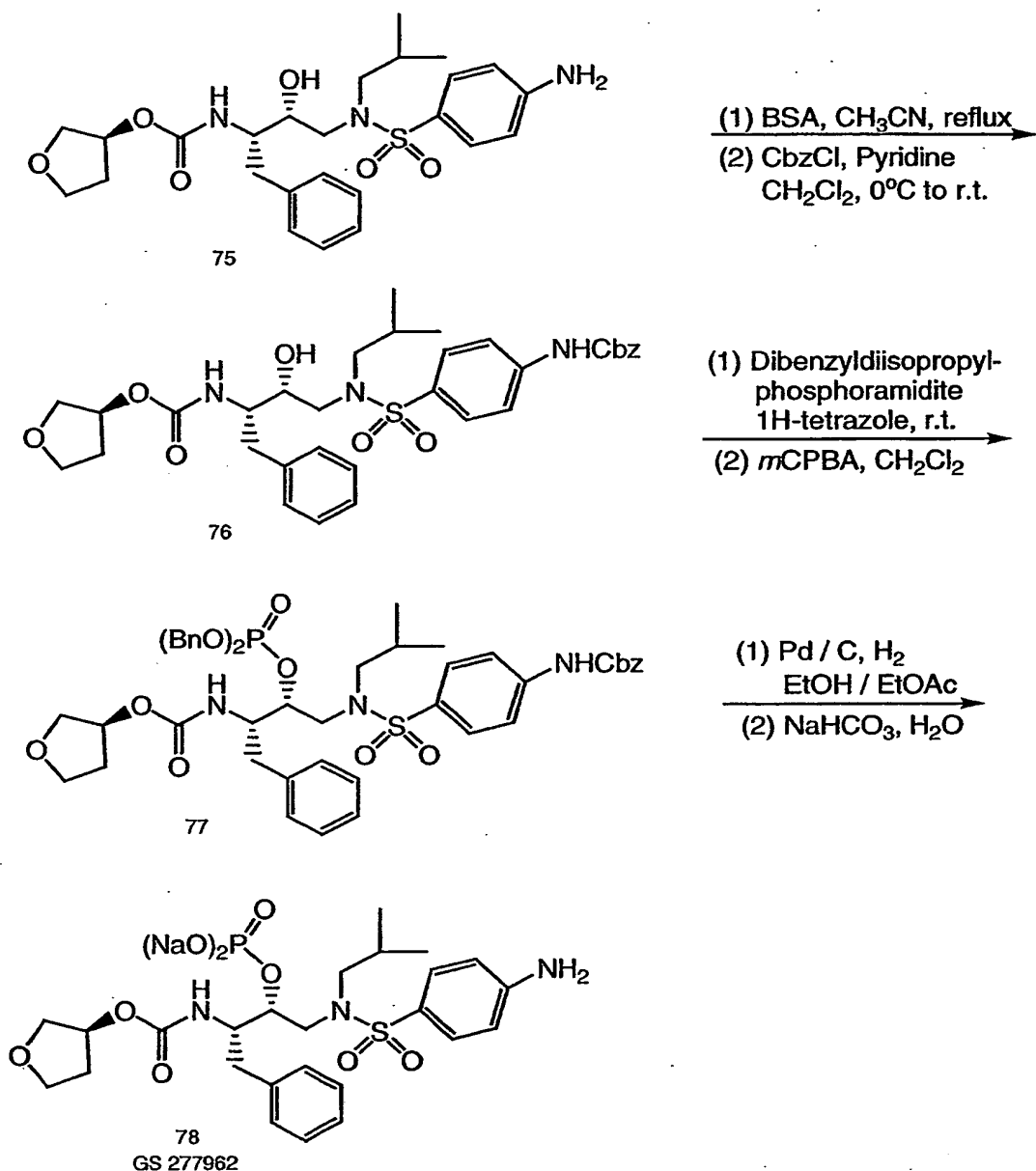
Example 61

Monophospholactate 70: A solution of 59 (1.48 g, 1.74 mmol) and Boc-L-valine (0.38 g,
1.74 mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C was treated with 1,3- dicyclohexylcarbodiimide (0.45
g, 2.18 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol). The reaction mixture was
stirred at 0°C for 1 h and then warmed to room temperature for 2 h. The product was

partitioned between CH₂Cl₂ and 0.2 N HCl. The organic layer was washed with H₂O, dried
with Na₂SO₄, filtered, and concentrated. The crude product was purified by column
chromatography on silica gel (4% 2-propanol/CH₂Cl₂) to give the monophospholactate (1.65
g, 90%) as a white solid.

5

Example 62

Monophospholactate 71: A solution of 70 (1.65 g, 1.57 mmol) in CH₂Cl₂ (8 mL) at 0°C was
treated with trifluoroacetic acid (4 mL). The solution was stirred for 30 min at 0°C and then
warmed to room temperature for an additional 30 min. The reaction mixture was diluted with
10   toluene and concentrated under reduced pressure. The crude product was purified by column
chromatography on silica gel (10% 2-propanol/CH₂Cl₂) to give the monophospholactate
(1.42 g, 85%, GS 278635, 2/3 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl₃) δ
7.73 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.4-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.47 (m,
1H), 5.33-5.06 (m, 4H), 4.57-4.41 (m, 2H), 4.2 (m, 2H), 3.96-3.7 (m, 7H), 3.15-2.73 (m, 7H),
15   2.38 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H), 1.63-1.5 (m, 4H), 1.24 (m, 3H), 1.19 (m, 6H), 0.91
(d, 3H), 0.88 (d, 3H); ^{31}P NMR (CDCl₃) δ 17.3, 15.4.

Example 63

Monophospholactate 73: A solution of 72 (0.43 g, 0.50 mmol) and Boc-L-valine (0.11 g,
20   0.50 mmol) in CH₂Cl₂ (6 mL) was treated with 1,3-dicyclohexylcarbodiimide (0.13 g, 0.63
mmol) and 4-dimethylaminopyridine (62 mg, 0.5 mmol). The reaction mixture was stirred at
room temperature overnight. The product was partitioned between CH₂Cl₂ and 0.2 N HCl.
The organic layer was washed with H₂O, dried with Na₂SO₄, filtered, and concentrated. The
crude product was purified by column chromatography on silica gel (2% 2-propanol/CH₂Cl₂)
25   to give the monophospholactate (0.45 g, 85%) as a white solid.

Example 64

Monophospholactate 74: A solution of 73 (0.44 g, 0.42 mmol) in CH₂Cl₂ (1 mL) at 0°C was
treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and
30   then warmed to room temperature for an additional 30 min. The reaction mixture was diluted
with toluene and concentrated under reduced pressure. The crude product was purified by
column chromatography on silica gel (10% 2-propanol/CH₂Cl₂) to give the
monophospholactate (0.40 g, 90%, GS 278785, 1:1 diastereomeric mixture) as a white solid:

-1400-

^{1}H NMR (CDCl3) δ 7.69 (d, J = 8.4 Hz, 2H), 7.34-7.2 (m, 7H), 6.98 (d, J = 8.4 Hz, 2H), 6.88 (m, 2H), 6.16 (m, 1H), 5.64 (m, 1H), 5.46 (m, 1H), 5.2-5.0 (m, 2H), 4.5 (m, 2H), 4.2 (m, 3H), 4.0-3.4 (m, 9H), 3.3 (m, 1H), 3.0-2.8 (m, 5H), 2.5 (m, 1H), 1.83 (m, 1H), 1.6-1.5 (m, 5H), 1.25 (m, 3H), 1.15 (m, 6H), 0.82 (d, J = 6.0 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H); ^{31}P NMR
(CDCl3) δ 17.3, 15.5.

Example 65

Cbz Amide 76: Compound 75 (0.35 g, 0.69 mmol) was dissolved in CH3CN (6 mL). N,O-Bis(trimethylsilyl)acetamide (BSA, 0.67 mL, 2.76 mmol) was added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in CH2Cl2 (3 mL) and cooled to 0°C. Pyridine (0.17 mL, 2.07 mmol) and benzyl chloroformate (0.12 mL, 0.83 mmol) were added. The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature overnight. The reaction was quenched with MeOH (5 mL) and 10% HCl (20 mL) at 0°C and stirred for 1 h. The product was extracted with CH2Cl2, washed with brine, dried with Na2SO4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH2Cl2) to give the CBz amide (0.40 g, 90%) as a white solid.

Example 66

Dibenzylphosphonate 77: A solution of 76 (0.39 g, 0.61 mmol) and 1H-tetrazole (54 mg, 0.92 mmol) in CH2Cl2 (8 mL) was treated with dibenzyldiisopropylphosphoramidite (0.32 g, 0.92 mmol) and stirred at room temperature overnight. The solution was cooled to 0°C, treated with mCPBA, stirred for 1 h at 0°C and then warmed to room temperature for 1 h. The reaction mixture was poured into a mixture of aqueous Na2SO3 and NaHCO3 and extracted with CH2Cl2. The organic layer was washed with H2O, dried with Na2SO4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH2Cl2) to give the dibenzylphosphonate (0.42 g, 76%) as a white solid.

Example 67

Disodium Salt of Phosphonic Acid 78: To a solution of 77 (0.18 g, 0.20 mmol) in EtOH (20 mL) and EtOAc (4 mL) was added 10% Pd/C (40 mg). The suspension was stirred under H2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through

a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (0.11 g, 95%) which was dissolved in H_2O (4 mL) and treated with $NaHCO_3$ (32 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 1 h and lyopholyzed overnight to give the disodium salt of phosphonic acid (0.12 g, 99%, GS

5   277962) as a white solid: ^{1}H NMR (D_2O) δ 7.55 (dd, 2H), 7.2 (m, 5H), 7.77 (dd, 2H), 4.65 (m, 1H), 4.24 (m, 1H), 4.07 (m, 1H), 3.78-2.6 (m, 12H), 1.88-1.6 (m, 3H), 0.75 (m, 6H).

Scheme 1
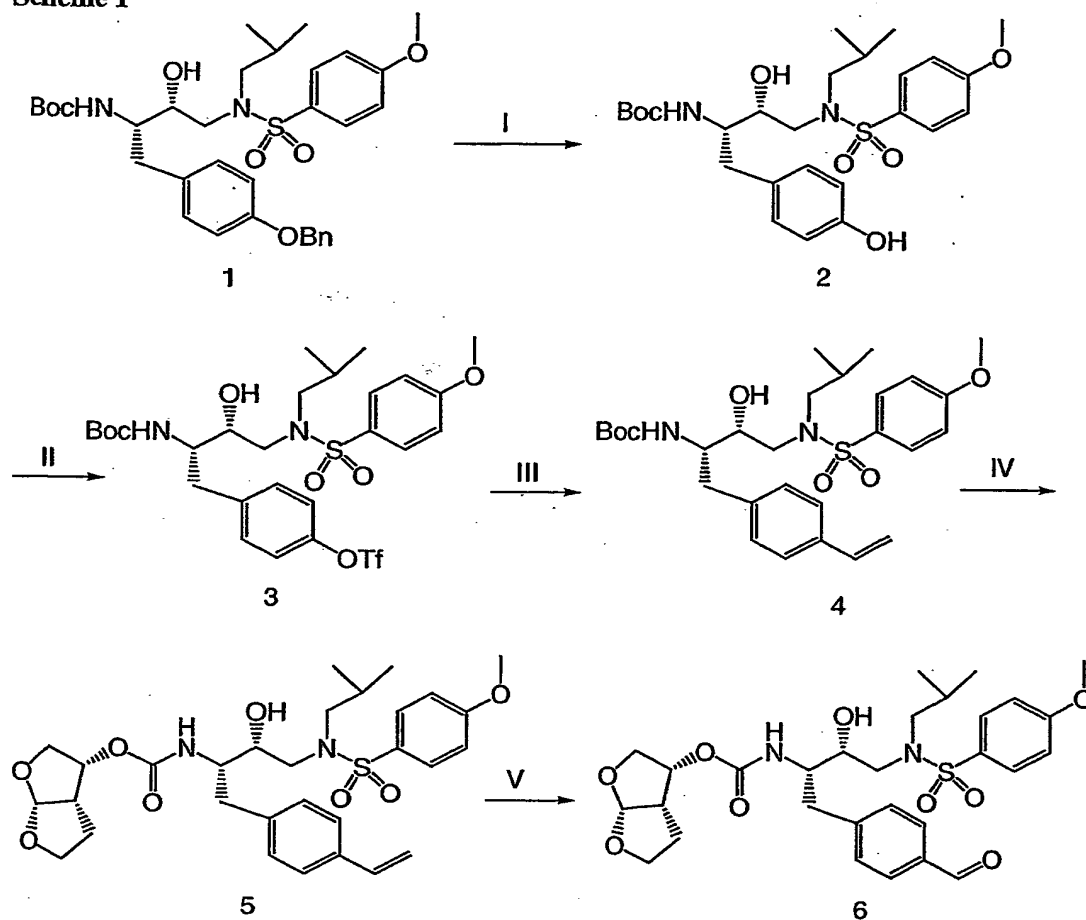
I. H$_2$/10%Pd-C/EtOAc-EtOH ; II.Tf$_2$NPh/Cs$_2$CO$_3$;
III. Bu$_3$SnCH=CH$_2$/PdCl$_2$(PPh$_3$)$_2$/LiCl/DMF/90 C;
IV.a. TFA/CH$_2$Cl$_2$;b.Bisfurancarbonate/i-Pr$_2$NEt/DMAP;
V.NaIO$_4$/OsO$_4$/EtOAc-H$_2$O

Example 1

5   Compound 1 was prepared by methods from Examples herein.

Example 2

Compound 2: To a solution of compound 1 (47.3 g) in EtOH/EtOAc (1000 mL/500 mL) was
added 10% Pd-C (5 g). The mixture was hydrogenated for 19 hours. Celite was added and

the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and was washed with ethyl acetate. Concentration gave compound 2 (42.1 g).

Example 3

5   Compound 3: To a solution of compound 2 (42.3 g, 81 mmol) in CH_2Cl_2 (833 mL) was added N-phenyltrifluoromethanesulfonimide (31.8 g, 89 mmol), followed by cesium carbonate (28.9 g, 89 mmol). The mixture was stirred for 24 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over $MgSO_4$. Purification by flash

10   column chromatography (CH_2Cl_2/EtOAc = 13/1) gave compound 3 (49.5 g) as a white powder.

Example 4

Compound 4: To a solution of compound 3 (25.2, 38.5 mmol) in DMF (240 mL) was added

15   lithium chloride (11.45 g, 270 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (540 mg, 0.77 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (11.25 mL). The reaction mixture was heated at 90°C for 6 hours and cooled to 25°C. Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The

20   combined organic layer was washed with water (6x) and brine, and dried over $MgSO_4$. Concentration gave an oil. The oil was diluted with dichloromethane (40 mL), water (0.693 mL, 38.5 mmol) and DBU (5.76 mL, 38.5 mmol) were added . The mixture was stirred for 5 minutes, and subjected to flash column chromatography (hexanes/EtOAc = 2.5/1). Compound 4 was obtained as white solid (18.4 g).

25

Example 5

Compound 5: To a solution of compound 4 (18.4 g, 34.5 mmol) in CH_2Cl_2 (70 mL) at 0°C was added trifluoroacetic acid (35 mL). The mixture was stirred at 0°C for 2 hrs, and solvents were evaporated under reduced pressure. The reaction mixture was quenched with

30   saturated sodium carbonate solution, and was extracted with ethyl acetate (3x). The combined organic layer was washed with saturated sodium carbonate solution(1x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration gave a solid. To a solution of the above solid in acetonitrile (220 mL) at 0°C was added bisfurancarbonate (10.09 g, 34.2

mmol), followed by di-isopropylethylamine (12.0 mL, 69.1 mmol) and DMAP (843 mg, 6.9 mmol). The mixture was warmed to 25°C and stirred for 12 hours. Solvents were removed under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2X), 5% hydrochloric acid (2x), water (2x), 1N sodium hydroxide (2x), water (2x),

5   and brine (1x), and dried over MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 1/1)) gave compound 5 (13.5 g).

Example 6

Compound 6: To a solution of compound 5 (13.5 g, 23 mmol) in ethyl acetate (135 mL) was

10   added water (135 mL), followed by 2.5% osmium tetraoxide/tert-butanol (17 mL). Sodium periodate (11.5 g) was added in portions over 2 minutes period. The mixture was stirred for 90 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = ½) gave compound 6 as white powder (12 g): ^{1}H NMR

15   (CDCl₃) δ 9.98 (1 H, s), 7.82 (2 H, m), 7.75 (2 H, m), 7.43 (2 H, m), 6.99 (2 H, m), 5.64 (1 H, m), 5.02 (2 H, m), 4.0-3.8 (9 H, m), 3.2-2.7 (7 H, m), 1.9-1.4 (3 H, m), 0.94 (6 H, m).

Scheme 2
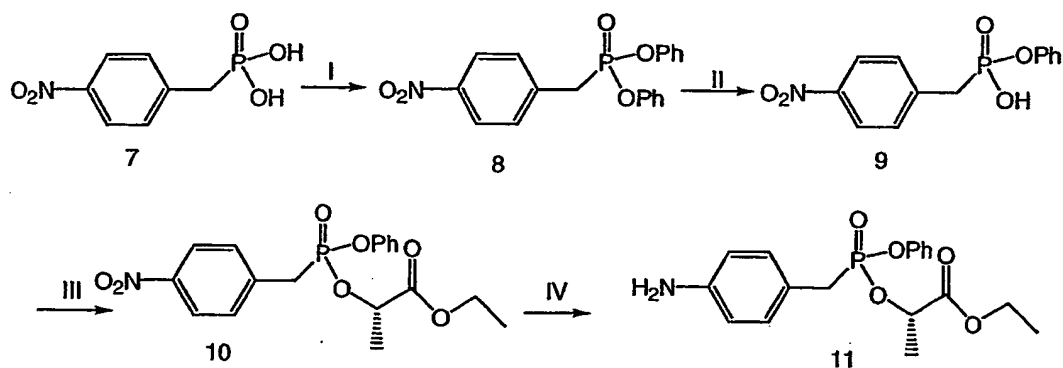
I. a..SOCl₂/toluene/60 C; b. PhOH/pyridine; II. a.NaOH/THF/H₂O; b. HCl;
III. b.SOCl₂/toluene/60 C; c.ethyl lactate/pyridine; IV. H₂/10%Pd-C/EtOAc

Scheme 3
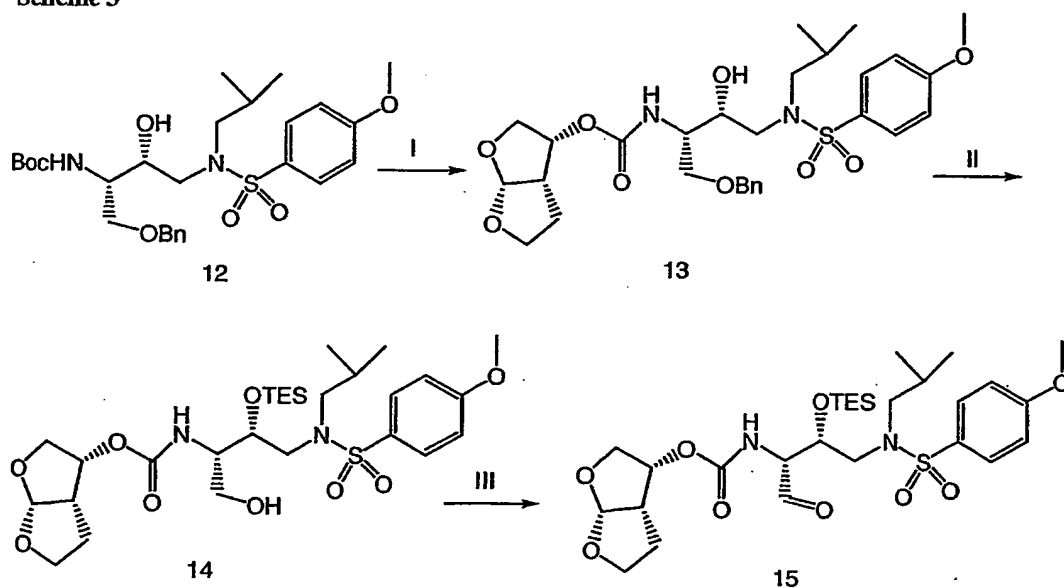
I. a.TFA/CH₂Cl₂; b. bisfurancarbonate/i-Pr₂NEt/DMAP; II. a.Et₃SiCl/Imidazole/DMF;
b. H₂/20%Pd(OH)₂-C/iPrOH; III. Des-Martin reagent/CH₂Cl₂

Scheme 4

11 + 15 ——I——▶

16

——II——▶

17
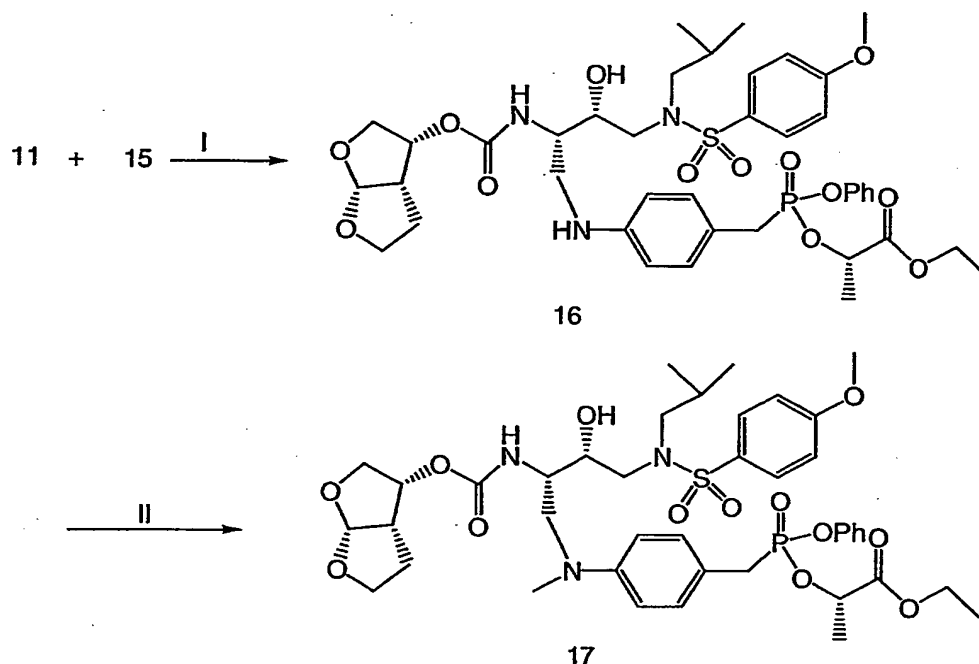
I. a. NaBH₃CN/HOAc/EtOAc; b. 2%HF/CH₃CN;
II. HCHO/NaBH₃CN/HOAc/EtOAc

Example 8

Compound 8: To the suspension of compound 7 (15.8 g, 72.5 mmol) in toluene (140 mL)

was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction

mixture was heated at 60°C for 5 hrs, and evaporated under reduced pressure. The mixture

was coevaporated with toluene (2x), EtOAc, and CH₂Cl₂ (2x) to afford a brown solid. To the

solution of the brown solid in CH₂Cl₂ at 0°C was added phenol (27.2 g, 290 mmol), followed

by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm

to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture

was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO₄.

Concentration gave a dark oil, which was purified by flash column chromatography

(hexanes/EtOAc = 4/1 to 1/1) to afford compound 8 (12.5 g).

Example 9

Compound 9: To a solution of compound 8 (2.21 g, 6 mmol) in THF (30 mL) was added 12 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and acetic acid (343 mL, 6 mmol) was added. The aqueous phase was washed with EtOAc (3x), and then

5   acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO$_4$. Concentration under reduced pressure gave compound 9 as a solid (1.1 g).

Example 10

10   Compound 10: To a suspension of compound 9 (380 mg, 1.3 mmol) in toluene (2.5 mL) was added thionyl chloride (1 mL, 13 mmol), followed by DMF (1 drop). The mixture was heated at 60°C for 2 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) and CH$_2$Cl$_2$ to give a white solid. To the solution of the above solid in CH$_2$Cl$_2$ (5 ml) at –20°C was added ethyl lactate (294 µL, 2.6

15   mmol), followed by pyridine (420 µL, 5.2 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure to give a yellow solid, which was purified by flash column chromatography to generate compound 10 (427 mg).

20   ## Example 11

Compound 11: To a solution of compound 10 (480 mg) in EtOAc (20 mL) was added 10% Pd-C (80 mg). The reaction mixture was hydrogenated for 6 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 11 (460 mg).

25

Example 12

Compound 12 was prepared by the methods of the Examples herein

Example 13

30   Compound 13: To a solution of compound 12 (536 mg, 1.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The liquid was coevaporated with CH$_2$Cl$_2$ (3x) and EtOAc (3x) to give a brown solid. To the solution of above brown solid in acetonitrile (6.5 mL) at 0°C was

added bisfurancarbonate (295 mg, 1.0 mmol), followed by diisopropylethylamine (350 μL,

2.0 mmol) and DMAP (24 mg). The mixture was warmed to 25°C, and was stirred for 12 hrs.

The mixture was diluted with EtOAc, and was washed sequentially with water (2x), 0.5 N

HCl (2x), water (2x), 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over

5   MgSO$_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1) afford

compound 13 (540 mg).

Example 14

Compound 14: To a solution of compound 13 (400 mg, 0.67 mmol) in DMF (3 mL) was

10   added imidazole (143 mg, 2.10 mmol), followed by triethylchlorosilane (224 μL, 1.34

mmol). The mixture was stirred for 12 hours. The mixture was diluted with EtOAc, and was

washed with water (5x) and brine, and dried over MgSO$_4$. Purification by flash column

chromatography (hexanes/EtOAc = 2/1) gave a white solid (427 mg). To the solution of

above solid in isopropanol (18 mL) was added 20% palladium(II) hydroxide on carbon (120

15   mg). The mixture was hydrogenated for 12 hours. The mixture was stirred with celite for 5

mins, and filtered through a pad of celite. Concentration under reduced pressure gave

compound 14(360 mg).

Example 15

20   Compound 15: To a solution of compound 14 (101 mg, 0.18 mmol) in CH$_2$Cl$_2$ (5 mL) was

added Dess-Martin periodiane (136 mg, 0.36 mmol). The mixture was stirred for 1 hour.

Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 15 (98

mg).

25   Example 16

Compound 16: To a solution of compound 15 (50 mg, 0.08 mmol) in EtOAc (0.5 mL) was

added compound 11 (150 mg, 0.41 mmol). The mixture was cooled to 0°C, acetic acid (19

μL, 0.32 mmol) was added, followed by sodium cyanoborohydride (10 mg, 0.16 mmol). The

mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with

30   EtOAc, and was washed with water (3x) and brine, and was dried over MgSO$_4$.

Concentration gave a oil. To the solution of above oil in acetonitrile (2.5 mL) was added

48% HF/CH$_3$CN (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with

EtOAc. The organic phase was washed with water (3x) and brine (1x), and was dried over

MgSO$_4$. Purification by flash column chromatography (CH$_2$Cl$_2$/iPrOH = 100/3) gave compound 16 (50 mg): ^{1}H NMR (CDCl$_3$) δ 7.72 (2 H, d, J = 8.9 Hz), 7.15-7.05 (7 H, m), 7.30 (2 H, d, J = 8.9 Hz), 6.64 (2 H, m), 5.73 (1 H, m), 5.45 (1 H, m), 5.13 (1 H, m), 4.93 (1 H, m), 4.22-3.75 (11 H, m), 3.4 (4 H, m), 3.35-2.80 (5 H, m), 2.1-1.8 (3 H, m), 1.40-1.25 (6 H, m), 0.94 (6 H, m).

Example 17

Compound 17: To a solution of compound 16 (30 mg, 0.04 mmol) in EtOAc (0.8 mL) was added 37% formaldehyde (26 μL, 0.4 mmol). The mixture was cooled to 0°C, acetic acid (20 μL, 0.4 mmol) was added, followed by sodium cyanoborohydride (22 mg, 0.4 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with water (3x) and brine, and was dried over MgSO$_4$. Purification by flash column chromatography (CH$_2$Cl$_2$/iPrOH = 100/3) gave compound 17 (22 mg): ^{1}H NMR (CDCl$_3$) δ 7.63 (2 H, m), 7.3-6.9 (9 H, m), 6.79 (2 H, m), 5.68 (1 H, m), 5.2 (1 H, m), 5.10 (1 H, m), 4.95 (1 H, m), 4.22 (2 H, m), 4.2-3.7 (21 H, m), 2.0-1.7 (3 H, m), 1.4-1.2 (6 H, m), 0.93 (6 H, m).

Scheme 5
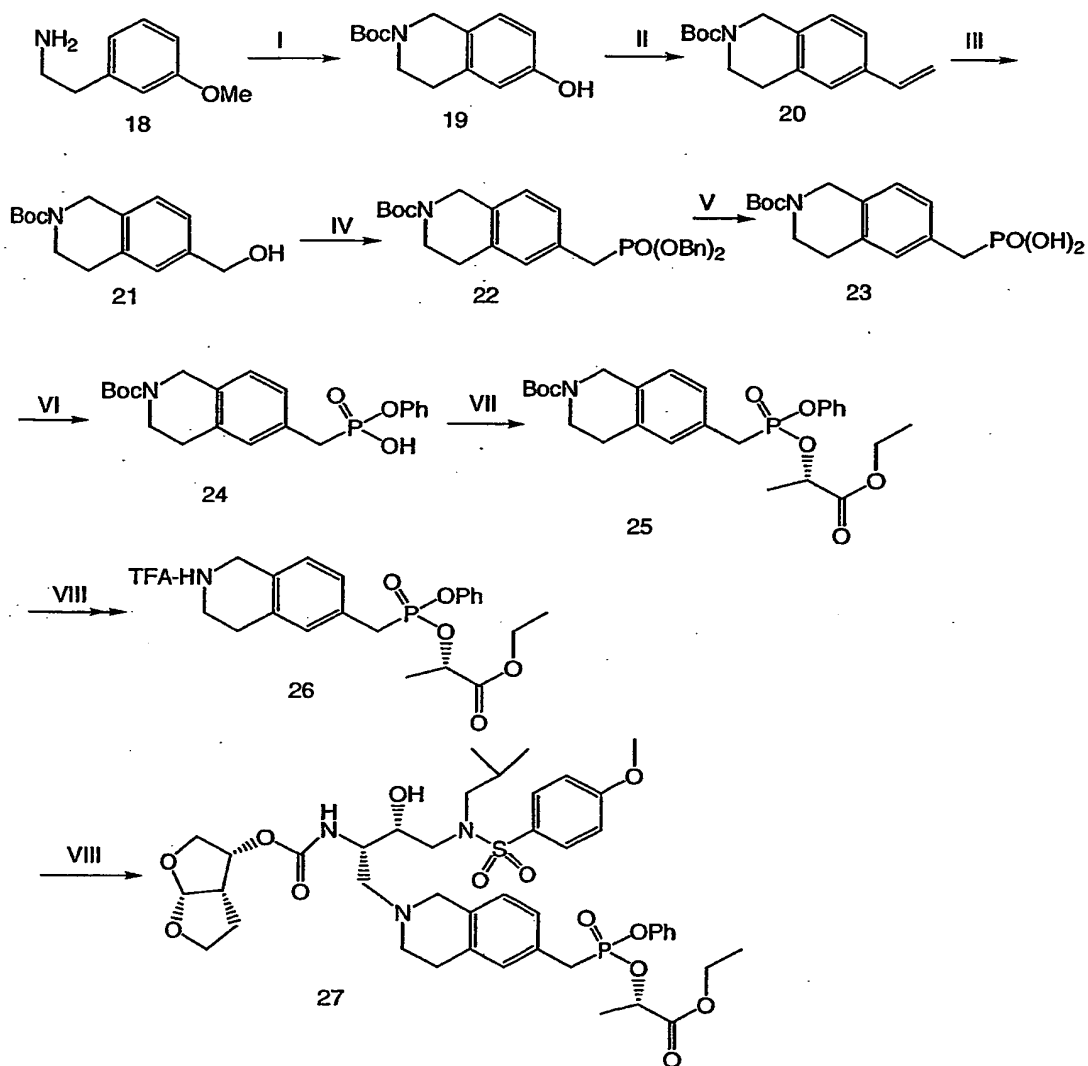
I. a.HCHO/100 C; b. HCl/100 C; c.HBr/120 C;d. Boc$_2$O/Na$_2$CO$_3$ II. a.Tf$_2$NPh/Cs$_2$CO$_3$;
b. Bu$_3$SnCH=CH$_2$/LiCl/PdCl$_2$(PPh$_3$)$_2$/90 C; III.a. NaIO$_4$/OsO$_4$; b. NaBH$_4$;
IV. a. CBr$_4$/PPh$_3$; b. (BnO)$_2$POH/Cs$_2$CO$_3$; V. H$_2$/10% Pd-C;VI. a. PhOH/DCC; b. NaOH; C. HCl;
VII. Ethyl lactate/BOP; VIII.TFA/CH$_2$Cl$_2$; VIII. compound 15/NaBH$_3$CN/HOAc.

Example 18

Compound 18: Compound 18 was purchased from Aldrich.

5

Example 19

Compound 19: To compound 18 (12.25 g, 81.1 mmol) was added 37% formaldehyde (6.15

mL, 82.7 mmol) slowly. The mixture was heated at 100°C for 1 hour. The mixture was

cooled to 25°C, and was diluted with benzene, and was washed with water (2x).

Concentration under reduced pressure gave a yellow oil. To above oil was added 20% HCl

5   (16 mL), and the mixture was heated at 100°C for 12 hours. The mixture was basified with

40% KOH solution at 0°C, and was extracted with EtOAc (3x). The combined organic layer

was washed with water and brine, and was dried over MgSO$_4$. Concentration gave a oil. To

the oil was added 48% HBr (320 mL), and the mixture was heated at 120°C for 3 hours.

Water was removed at 100°C under reduced pressure to give a brown solid. To the solution

10   of above solid in water/dioxane (200 mL/200mL) at 0°C was added sodium carbonate (25.7

g, 243 mmol) slowly, followed by di-tert-butyl dicarbonate (19.4 g, 89 mmol). The mixture

was warmed to 25°C and stirred for 12 hours. Dioxane was removed under reduced pressure,

and the remaining was extracted with EtOAc (3x). The combined organic phase was washed

with water (3x) and brine, and was dried over MgSO$_4$. Purification by flash column

15   chromatography (hexanes/EtOAc = 4/1 to 3/1) gave compound 19 as white solid (13.6 g).

Example 20

Compound 20: To a solution of compound 19 (2.49 g, 10 mmol) in CH$_2$Cl$_2$ (100 mL) was

added N-phenyltrifluoromethanesulfonimide (3.93 g, 11 mmol), followed by cesium

20   carbonate (3.58 g, 11 mmol). The mixture was stirred for 48 hours. The solvent was

removed under reduced pressure, and ethyl acetate was added. The reaction mixture was

washed with water (3x) and brine (1x), and was dried over MgSO$_4$. Purification by flash

column chromatography (hexanes/EtOAc = 6/1) gave a white solid (3.3 g). To the solution

of above solid (2.7 g, 7.1 mmol) in DMF (40 mL) was added lithium chloride (2.11 g, 49.7

25   mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (100 mg, 0.14 mmol).

The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To

the above solution was added tributylvinyltin (2.07 mL, 7.1 mmol). The reaction mixture

was heated at 90°C for 3 hours and cooled to 25°C. Water was added to the reaction, and the

mixture was extracted with ethyl acetate (3X). The combined organic layer was washed with

30   water (6x) and brine, and dried over MgSO$_4$. Concentration gave an oil. The oil was diluted

with CH$_2$Cl$_2$ (5 mL), water (128 μL, 7.1mmol) and DBU (1 mL, 7.1 mmol) were added. The

mixture was stirred for 5 minutes, and was subjected to flash column chromatography

(hexanes/EtOAc = 9/1). Compound 20 was obtained as white solid (1.43 g).

Example 21

Compound 21: To a solution of compound 20 (1.36 g, 5.25 mmol) in ethyl acetate (16 mL) was added water (16 mL), followed by 2.5% osmium tetraoxide/tert-butanol (2.63 mL).

5   Sodium periodate (2.44 g) was added in portions over 2 minutes period. The mixture was stirred for 45 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave a brown solid. To the solution of above solid in methanol (100 mL) at $0°C$ was added sodium borohydride. The mixture was stirred for 1 hour at $0°C$, and was quenched with saturated

10   NH_4Cl (40 mL). Methanol was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 21 (1.0 g).

15   Example 22

Compound 22: To a solution of compound 21 (657 mg, 2.57 mmol) in CH_2Cl_2 (2 mL) was added a solution of tetrabromocarbon (1.276 g, 3.86 mmol) in CH_2Cl_2 (2 mL). To the above mixture was added a solution of triphenylphsophine (673 mg, 2.57 mmol) in CH_2Cl_2 (2 mL) over 30 minutes period. The mixture was stirred for 2 hours, and was concentrated under

20   reduced pressure. Purification by flash column chromatography (hexanes/EtOAc = 9/1) gave the bromide intermediate (549 mg). To the solution of above bromide (548 mg, 1.69 mmol) in acetonitrile (4.8 mL) was added dibenzyl phosphite (0.48 mL, 2.19 mmol), followed by cesium carbonate (828 mg, 2.54 mmol). The mixture was stirred for 48 hours, and was diluted with EtOAc.

25   The mixture was washed with water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 100% EtOAc) gave compound 22 (863 mg).

Example 23

30   Compound 23: To a solution of compound 22 (840 mg) in ethanol (80 mL) was added 10% palladium on carbon (200 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 23 (504 mg).

-1413-

Example 24

Compound 24: To a solution of compound 23 (504 mg, 1.54 mmol) in pyridine (10.5 mL) was added phenol (1.45 g, 15.4 mmol), followed by DCC (1.28 g, 6.2 mmol). The mixture

5   was heated at 65°C for 3 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 ml), and was filtered and washed with EtOAc (2x5 mL). Concentration gave a oil, which was purified by flash column chromatography (CH$_2$Cl$_2$/isopropanol = 100/3) to give diphenylphosphonate intermediate (340 mg). To a solution of above compound (341 mg, 0.71 mmol) in THF (1 mL) was added 0.85 mL of 1.0

10 N NaOH solution. The mixture was stirred at 25°C for 3 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x), and then acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO$_4$. Concentration under reduced pressure gave compound 24 as a solid (270

15 mg).

Example 25:

Compound 25: To a solution of compound 24 (230 mg, 0.57 mmol) in DMF (2 mL) was added ethyl (s)-lactate (130 μL, 1.14 mmol), followed by diisopropylethylamine (400 μL,

20 2.28 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (504 mg, 1.14 mmol). The mixture was stirred for 14 hours, was diluted with EtOAc. The organic phase was washed with water (5x) and brine (1x), and was dried over MgSO$_4$. Purification by flash column chromatography (CH$_2$Cl$_2$/isopropanol = 100/3) gave compound 25 (220 mg).

25

Example 26

Compound 26: To a solution of compound 25 (220 mg) in CH$_2$Cl$_2$ (2 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The mixture was diluted with EtOAc, and was washed with saturated

30 sodium carbonate solution, water, and brine, and was dried over MgSO$_4$. Concentration gave compound 26 (170 mg).

Example 27

Compound 27: To a solution of compound 15 (258 mg, 0.42 mmol) in EtOAc (2.6 mL) was added compound 26 (170 mg, 0.42 mmol), followed by acetic acid (75 μL, 1.26 mmol). The mixture was stirred for 5 minutes, and sodium cyanoborohydride (53 mg, 0.84 mmol) was added. The mixture was stirred for 14 hrs. The mixture was diluted with EtOAc, and was

5   washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/4 to 100/6) gave the intermediate (440 mg). To the solution of above compound (440 mg) in acetonitrile (10 mL) was added 48% HF/ CH_3CN (0.4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc,

10   and was washed with water (3x) and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 27 (120 mg): ^1H NMR ($CDCl_3$) δ 7.70 (2 H, m), 7.27 (2 H, m), 7.15 (5 H, m), 6.95 (3 H, m), 5.73 (1 H, m), 5.6-5.4 (1 H, m), 5.16 (1 H, m), 4.96 (1 H, m), 4.22-3.60 (13 H, m), 3.42 (2 H, m), 3.4-2.6 (11 H, m), 2.1-3.8 (3 H, m), 1.39 (3 H, m), 1.24 (3 H, m), 0.84 (6 H, m).

15

Scheme 6
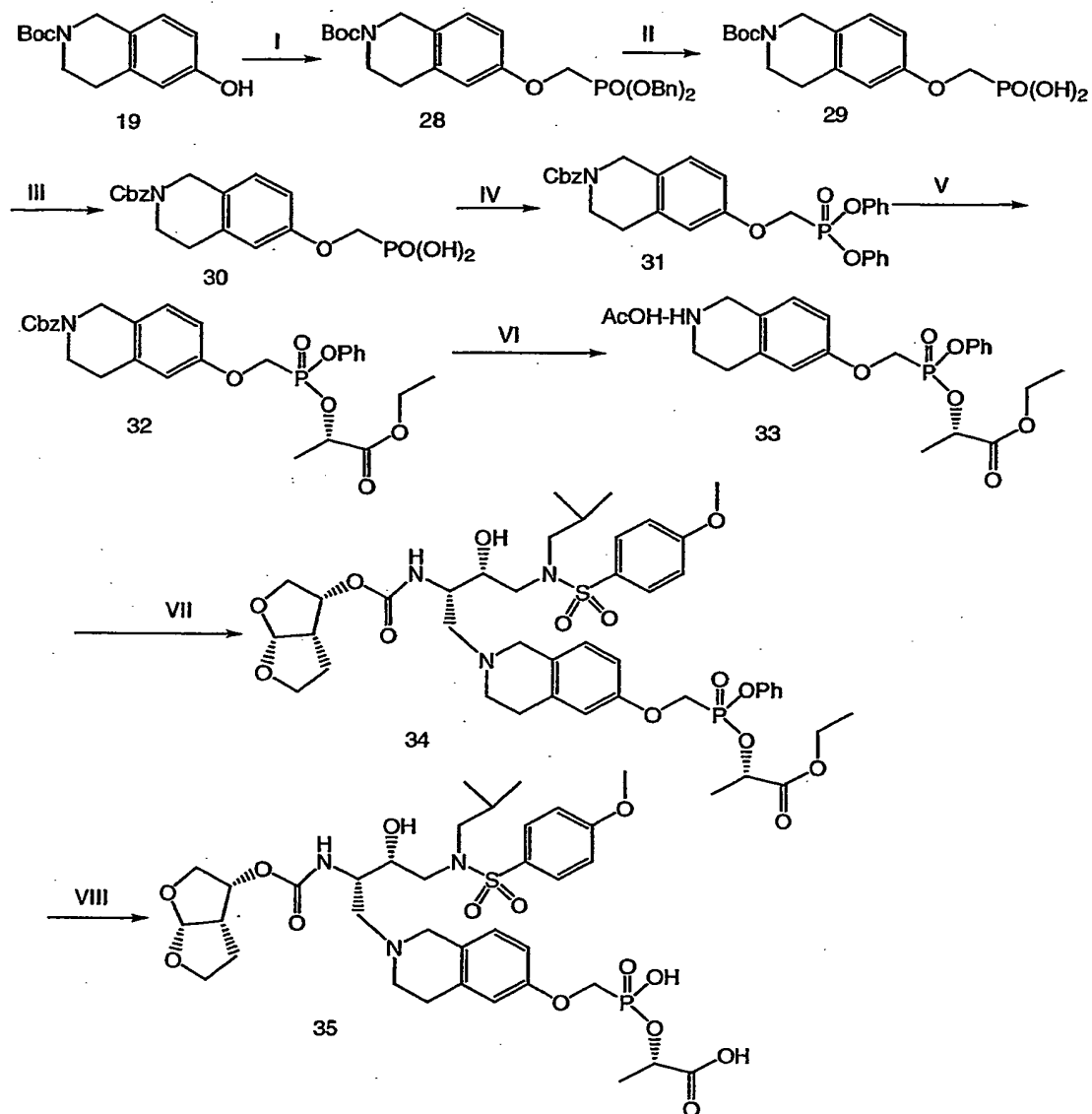
I. TfOCH$_2$PO(OBn)$_2$/Cs$_2$CO$_3$ II.H$_2$/10% Pd-C; III.a. TFA/CH$_2$Cl$_2$;
b.CbzCl/NaOH; IV. a.SOCl$_2$/60 C;b. PhOH/pyridine; V. a. NaOH/THF;
b. HCl; c. SOCl$_2$/60 C; d. Ethyl (s)Lactate/pyridine; VI. H$_2$/10% Pd-C/HOAc;
VII.a. compound 15/NaBH$_3$CN/HOAc; b. 2%HF/CH$_3$CN;
VIII. esterase/1.0 PBS buffer/CH$_3$CN/DMSO

Example 28

Compound 28: To a solution of compound 19 (7.5 g, 30 mmol) in acetonitrile (420 mL) was
5 added dibenzyl triflate (17.8 g, 42 mmol), followed by cesium carbonate (29.4 g, 90 mmol).

The mixture was stirred for 2.5 hours, and was filtered. Acetonitrile was removed under

reduced pressure, and the remaining was diluted with EtOAc. The mixture was washed with

water (3x) and brine, and was dried over MgSO₄. Purification by flash column

chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 28 (14.3 g).

5

Example 29

Compound 29: To a solution of compound 28 (14.3 g) in ethanol (500 mL) was added 10%

palladium on carbon (1.45 g). The mixture was hydrogenated for 2 hours. The mixture was

stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under

10   reduced pressure gave compound 29 (9.1 g).

Example 30

Compound 30: To a solution of compound 29 (9.1 g) in CH₂Cl₂ (60 mL) was added

trifluoroacetic acid (30 mL). The mixture was stirred for 4 hrs, and was concentrated under

15   reduced pressure. The mixture was coevaporated with CH₂Cl₂ (3x) and toluene, and was

dried under high vacuum to give a white solid. The white solid was dissolved in 2.0 N NaOH

solution (45 mL, 90 mmol), and was cooled to 0°C. To the above solution was added slowly

a solution of benzyl chloroformate (6.4 mL, 45 mmol) in toluene (7 mL). The mixture was

warmed to 25°C, and was stirred for 6 hours. 2.0 N sodium hydroxide was added to above

20   solution until pH =11. The aqueous was extracted with ethyl ether (3x), and was cooled to

0°C. To the above aqueous phase at 0°C was added concentrated HCl until pH = 1. The

aqueous was extracted with EtOAc (3x). The combine organic layers were washed with

brine, and were dried over MgSO₄. Concentration gave compound 30 (11.3 g) as a white

solid.

25

Example 31

Compound 31: To the suspension of compound 30 (11.3 g, 30 mmol) in toluene (150 mL)

was added thionyl chloride (13 mL, 180 mmol), followed by DMF (a few drops). The

reaction mixture was heated at 65°C for 4.5 hrs, and evaporated under reduced pressure. The

30   mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the

brown solid in CH₂Cl₂ (120 ml) at 0°C was added phenol (11.28 g, 120 mmol), followed by

slow addition of pyridine (14.6 mL, 180 mmol). The reaction mixture was allowed to warm

to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture

was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO₄. Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) to afford compound 31 (9.8 g).

5   Example 32

Compound 32: To a solution of compound 31 (9.8 g, 18.5 mmol) in THF (26 mL) was added 20.3 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2.5 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to 0°C, and was acidified with concentrated

10   HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO₄. Concentration under reduced pressure gave a solid (8.2 g). To a suspension of above solid (4.5 g, 10 mmol) in toluene (50 mL) was added thionyl chloride (4.4 mL, 60 mmol), followed by DMF (0.2 mL). The mixture was heated at 70°C for 3.5 hours. The solvent and reagent were removed under

15   reduced pressure. The mixture was coevaporated with toluene (2x) to give a white solid. To the solution of the above solid in CH₂Cl₂ (40 mL) at 0°C was added ethyl (s)-lactate (2.3 mL, 20 mmol), followed by pyridine (3.2 mL, 40 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was

20   dried over MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 32 (4.1 g).

        Example 33

Compound 33: To a solution of compound 32 (3.8 g, 6.9 mmol) in EtOAc/EtOH (30 mL/30

25   mL) was added 10% palladium on carbon (380 mg), followed by acetic acid (400 μL, 6.9 mmol). The mixture was hydrogenated for 3 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 33 (3.5 g).

30   Example 34

Compound 34: To a solution of compound 15 (1.70 g, 2.76 mmol) in EtOAc (17 mL) was added compound 33 (3.50 g, 6.9 mmol). The mixture was stirred for 5 minutes, and was cooled to 0°C, and sodium cyanoborohydride (347 mg, 5.52 mmol) was added. The mixture

-1418-

was stirred for 6 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/6) gave the intermediate (3.4 g). To the solution of above compound (3.4 g) in acetonitrile (100 mL) was added 48% HF/ CH_3CN

5   (4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with saturated sodium carbonate, water (3x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 34 (920 mg): ^1H NMR ($CDCl_3$) δ 7.71 (2 H, m), 7.38-7.19 (5 H, m), 6.92 (3 H, m), 6.75 (2 H, m), 5.73 (1 H, m),

10   5.57-5.35 (1 H, m), 5.16 (2 H, m), 4.5 (2 H, m), 4.2-3.6 (13 H, m), 3.25-2.50 (11 H, m), 2.0-1.8 (3 H, m), 1.5 (3 H, m), 1.23 (3 H, m), 0.89 (6 H, m).

Example 35

Compound 35: To a solution of compound 34 (40 mg) in CH_3CN /DMSO (1 mL/0.5 mL)

15   was added 1.0 M PBS buffer (5 mL), followed by esterase (200 µL). The mixture was heated at 40°C for 48 hours. The mixture was purified by reverse phase HPLC to give compound 35 (11 mg).

Scheme 7
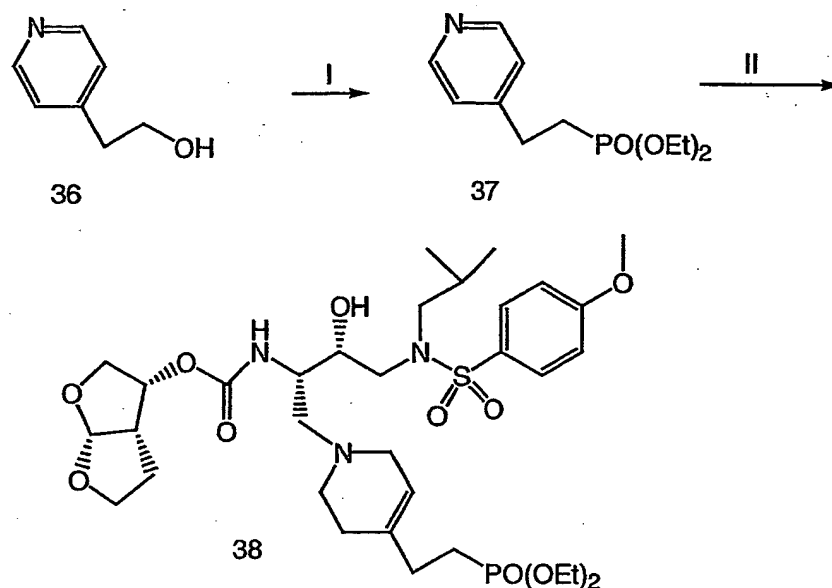
I. a.SOCl₂/toluene/60 C; b. P(OEt)₃/toluene/120 C;
II. a. compound 14/Tf₂O;b. NaBH₄/EtOH/HOAc; c. 2% HF/CH₃CN

Example 36

Compound 36: Compound 36 was purchased from Aldrich.

5

Example 37

Compound 37: To a solution of compound 36 (5.0 g, 40 mmol) in chloroform (50 mL) was
added thionyl chloride (12 mL) slowly. The mixture was heated at 60°C for 2.5 hours. The
mixture was concentrated under reduced pressure to give a yellow solid. To the suspension

10   of above solid (5.2 g, 37 mmol) in toluene (250 mL) was added triethyl phosphite (19 mL,
370 mmol). The mixture was heated at 120°C for 4 hours, and was concentrated under
reduced pressure to give a brown solid. The solid was dissolved in EtOAc, and was basified
with 1.0 N NaOH. The organic phase was separated and was washed with water (2x) and
brine, and was dried over MgSO₄. Purification by flash column chromatography

15   (CH₂Cl₂/iPrOH = 9/1) gave compound 37 (4.8 g).

Example 38

Compound 38: To a solution of compound 14 (100 mg, 0.16 mmol) and compound 37 (232 mg, 0.74 mmol) in CH$_2$Cl$_2$ (1 mL) at −40°C was added triflic anhydride (40 µL, 0.24 mmol) slowly. The mixture was warmed to 25°C slowly, and was stirred for 12 hours. The mixture

5   was concentrated, and was diluted with EtOH/EtOAc (2 mL/0.4 mL). To the above solution at 0°C was added sodium borohydride (91 mg) in portions. The mixture was stirred at 0°C for 3 hours, and was diluted with EtOAc. The mixture was washed with saturated sodium bicarbonate, water, and brine, and was dried over MgSO$_4$. Purification by flash column chromatograph (CH$_2$Cl$_2$/iPrOH = 100/5 to 100/10) gave the intermediate (33 mg). To the

10   solution of above intermediate in acetonitrile (2.5 mL) was added 48% HF/ CH$_3$CN (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic solution was washed with 0.5 N sodium hydroxide, water, and brine, was dried over MgSO$_4$. Purification by reverse HPLC gave compound 38 (12 mg): ^{1}H NMR (CDCl$_3$) δ 7.72 (2 H, d, J = 8.9 Hz), 7.02 (2 H, d, J = 8.9 Hz), 5.70 (1 H, m), 5.45 (1 H, m), 5.05 (1 H, m), 4.2-3.4 (19

15   H, m), 3.4-2.8 (5 H, m), 2.45-2.20 (4 H, m), 2.15-1.81 (5 H, m), 1.33 (6 H, m), 0.89 (6 H, m).

Scheme 8
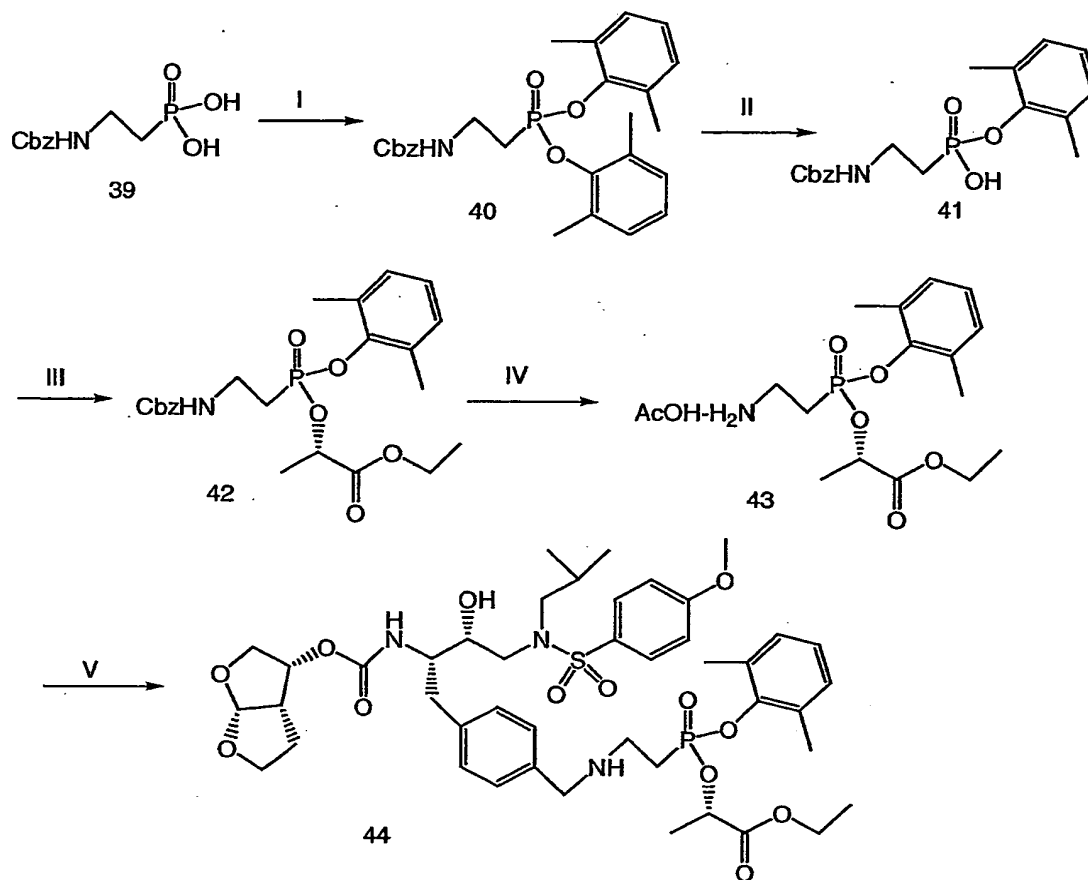
I. a..SOCl$_2$/toluene/60 C; b. ArOH/pyridine; II. a.NaOH/THF/H$_2$O; b. HCl;
III. b.SOCl$_2$/toluene/60 C; c.ethyl lactate/pyridine; IV. H$_2$/10%Pd-C/EtOAc/HOAc;
V. a. compound 6/MgSO$_4$; b. HOAc/NaCNBH$_3$

Example 39

Compound 39 was prepared by the methods of the previous Examples.

Example 40

Compound 40: To the suspension of compound 39 (4.25 g, 16.4 mmol) in toluene (60 mL)
was added thionyl chloride (7.2 mL, 99 mmol), followed by DMF (a few drops). The
reaction mixture was heated at 65°C for 5 hrs, and evaporated under reduced pressure. The
mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the
brown solid in CH$_2$Cl$_2$ (60 ml) at 0°C was added 2,6-dimethylphenol (8.1 g, 66 mmol),

followed by slow addition of pyridine (8mL, 99 mmol). The reaction mixture was allowed to

warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The

mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over

MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1)

5   afforded compound 40 (1.38 g).

Example 41

Compound 41: To a solution of compound 40 (1.38 g, 1.96 mmol) in THF (6 mL) was added

3.55 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 24 hours, and THF

10   was removed under reduced pressure. The mixture was diluted with water, and was washed

with EtOAc (3x). The aqueous phase was cooled to 0°C, and was acidified with concentrated

HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer

was washed with water (1x) and brine (1x), and dried over MgSO₄. Concentration under

reduced pressure gave compound 41 as a white solid (860 mg).

15

Example 42

Compound 42: To a suspension of compound 41 (1.00 g, 2.75 mmol) in toluene (15 mL) was

added thionyl chloride (1.20 mL, 16.5 mmol), followed by DMF (3 drops). The mixture was

heated at 65°C for 5 hours. The solvent and reagent were removed under reduced pressure.

20   The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the

above solid in CH₂Cl₂ (11 mL) at 0°C was added ethyl (s)-lactate (1.25, 11 mmol), followed

by pyridine (1.33 mL, 16.6 mmol). The mixture was warmed to 25°C and stirred for 12

hours. The reaction mixture was concentrated under reduced pressure, and was diluted with

EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over

25   MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave

compound 42 (470 mg).

Example 43

Compound 43: To a solution of compound 42 (470 mg) in EtOH (10 mL) was added 10%

30   palladium on carbon (90 mg), followed by acetic acid (150 μL). The mixture was

hydrogenated for 6 hours. The mixture was stirred with celite for 5 mins, and was filtered

through a pad of celite. Concentration under reduced pressure gave compound 43 (400 mg).

Example 44

Compound 44: To a solution of compound 6 (551 mg, 0.93 mmol) in 1,2-dichloroethane (4
mL) was added compound 43 (400 mg, 1.0 mmol), followed by MgSO₄ (1 g). The mixture
was stirred for 3 hours, and acetic acid (148 µL) and sodium cyanoborohydride (117 mg, 1.86
5   mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted
with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and
brine, and was dried over MgSO₄. Purification by flash column chromatography (EtOAc to
EtOAc/EtOH = 9/1) gave compound 44. Compound 44 was dissolved in CH₂Cl₂ (25 mL),
and trifluoroacetic acid (100 µL) was added. The mixture was concentrated to give
10   compound 44 as a TFA salt (560 mg): ^{1}H NMR (CDCl₃) δ 7.74 (2 H, m), 7.39 (2 H, m), 7.20
(2 H, m), 7.03 (5 H, m), 5.68 (1 H, m), 5.43 (1 H, m), 5.01 (1 H, m), 4.79 (1 H, m), 4.35-4.20
(4 H, m), 4.18-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.30 (6 H, m), 1.82 (1 H, m), 1.70 (2 H, m),
1.40-1.18 (6 H, m), 0.91 (6 H, m).

Scheme 9
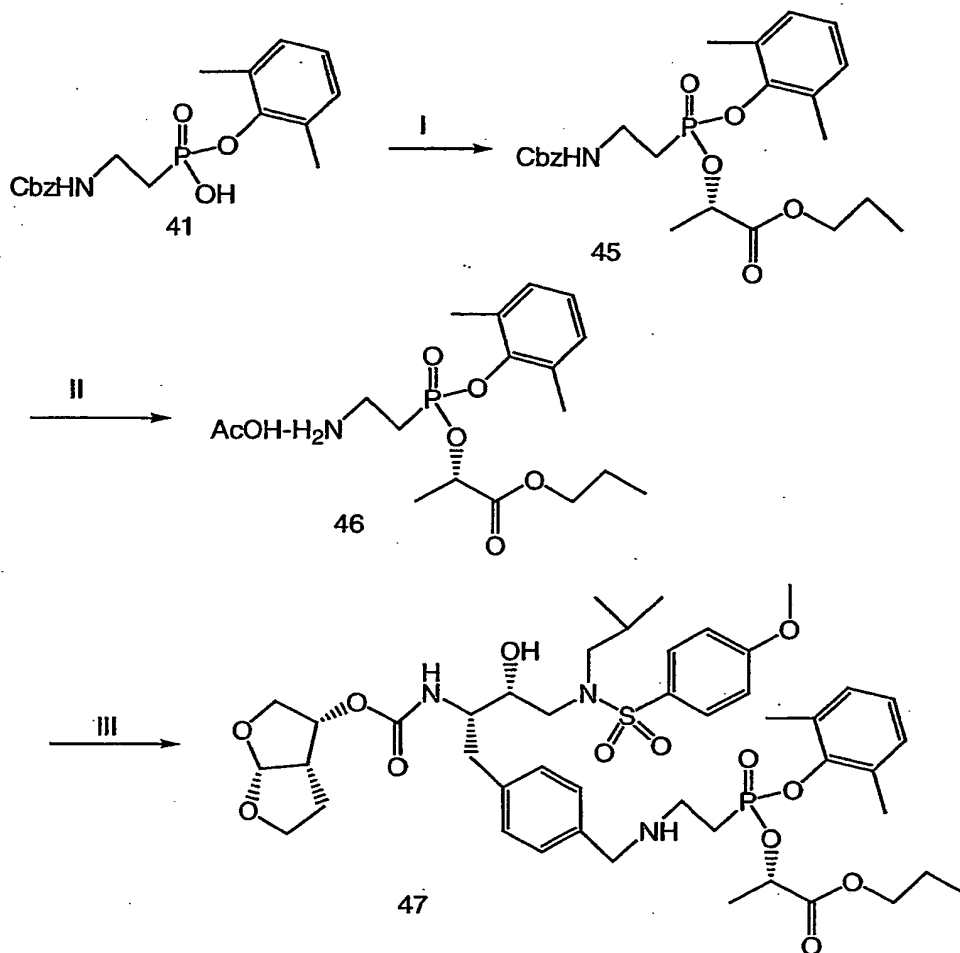
I. b.SOCl₂/toluene/60 C; c.propyl (s)-lactate/pyridine;
II. H₂/10%Pd-C/EtOAc/HOAc;
III. a. compound 6/MgSO₄; b. HOAc/NaCNBH₃

Example 45

Compound 45: To a suspension of compound 41 (863 mg, 2.4 mmol) in toluene (13 mL) was

5   added thionyl chloride (1.0mL, 14.3 mmol), followed by DMF (3 drops). The mixture was

heated at 65°C for 5 hours. The solvent and reagent were removed under reduced pressure.

The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the

above solid in CH₂Cl₂ (10 mL) at 0°C was added propyl (s)-lactate (1.2mL, 9.6 mmol),

followed by triethylamine (2.0 mL, 14.4 mmol). The mixture was warmed to 25°C and

10   stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was

diluted with EtOAc. The organic phase was washed with water and brine, and was dried over

MgSO$_4$. Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave

compound 45 (800 mg).

5   Example 46

Compound 46: To a solution of compound 45 (785 mg) in EtOH (17 mL) was added 10%

palladium on carbon (150 mg), followed by acetic acid (250 μL). The mixture was

hydrogenated for 16 hours. The mixture was stirred with celite for 5 mins, and was filtered

through a pad of celite. Concentration under reduced pressure gave compound 46 (700 mg).

10

Example 47

Compound 47: To a solution of compound 6 (550 mg, 0.93 mmol) in 1,2-dichloroethane (4

mL) was added compound 43 (404 mg, 1.0 mmol), followed by MgSO$_4$ (1 g). The mixture

was stirred for 3 hours, and acetic acid (148 μL) and sodium cyanoborohydride (117 mg, 1.86

15   mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted

with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and

brine, and was dried over MgSO$_4$. Purification by flash column chromatography (EtOAc to

EtOAc/EtOH = 9/1) gave compound 47. Compound 47 was dissolved in CH$_2$Cl$_2$ (25 mL),

and trifluoroacetic acid (100 μL) was added. The mixture was concentrated to give

20   compound 47 as a TFA salt (650 mg): ^{1}H NMR (CDCl$_3$) δ 7.74 (2 H, m), 7.41 (2 H, m),

7.25-7.1 (2 H, m), 7.02 (5 H, m), 5.65 (1 H, m), 5.50 (1 H, m), 5.0-4.75 (2 H, m), 4.25-4.05

(4 H, m), 4.0-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.31 (6 H, m), 1.82-1.51 (3 H, m), 1.45-1.2 (5

H, m), 0.93 (9 H, m).

Scheme 10

I. DCC/pyridine/60 C
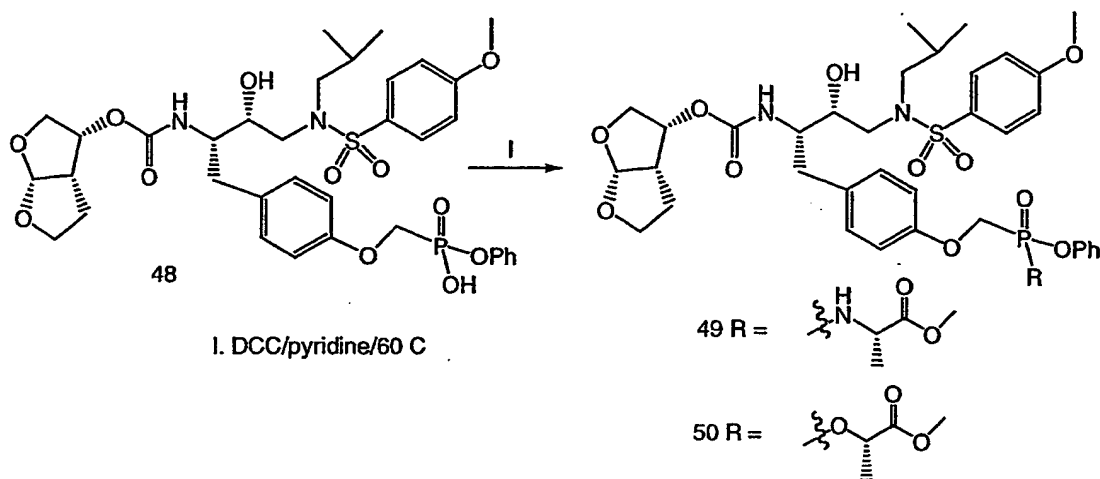
Example 48

Compound 48 was made by the methods of the previous Examples.

5

Example 49

Compound 49: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added L-alanine methyl ester hydrochloride (73 mg, 0.52 mmol), followed by DCC (161 mg, 0.78 mmol). The mixture was heated at 60°C for 1 hour. The mixture was diluted with

10   EtOAc, and was washed with 0.2 N HCl, water, 5% sodium bicarbonate, and brine, and was dried over MgSO₄. Purification by flash column chromatography (CH₂Cl₂/iPrOH = 100/5) gave compound 49 (46 mg): ¹H NMR (CDCl₃) δ 7.73 (2 H, m), 7.38-7.18 (7 H, m), 7.03 (2 H, m), 6.89 (2 H, m), 5.68 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.30 (3 H, m), 4.0-3.6 (12 H, m), 3.2-2.8 (7 H, m), 1.84-1.60 (3 H, m), 1.38 (3 H, m), 0.93 (6 H, m).

15

Example 50

Compound 50: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added methyl (s)-lactate (41 mg, 0.39 mmol), followed by DCC (81 mg, 0.39 mmol). The mixture was heated at 60°C for 2 hours, and pyridine was removed under reduced

20   pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH₂Cl₂/iPrOH = 100/5) gave compound 50 (83 mg): ¹H NMR (CDCl₃) δ 7.74 (2 H, m), 7.38-7.14 (7 H, m), 7.02 (2 H, m), 6.93 (2 H, m), 5.67 (1 H,

m), 5.18 (1 H, m), 5.04 (1 H, m), 4.92 (1 H, m), 4.5 (2 H, m), 4.0-3.68 (12 H, m), 3.2-2.75 (7 H, m), 1.82 (1 H, m), 1.75-1.50 (5 H, m), 0.93 (6 H, m).

Scheme 11

51 52 53

54

55
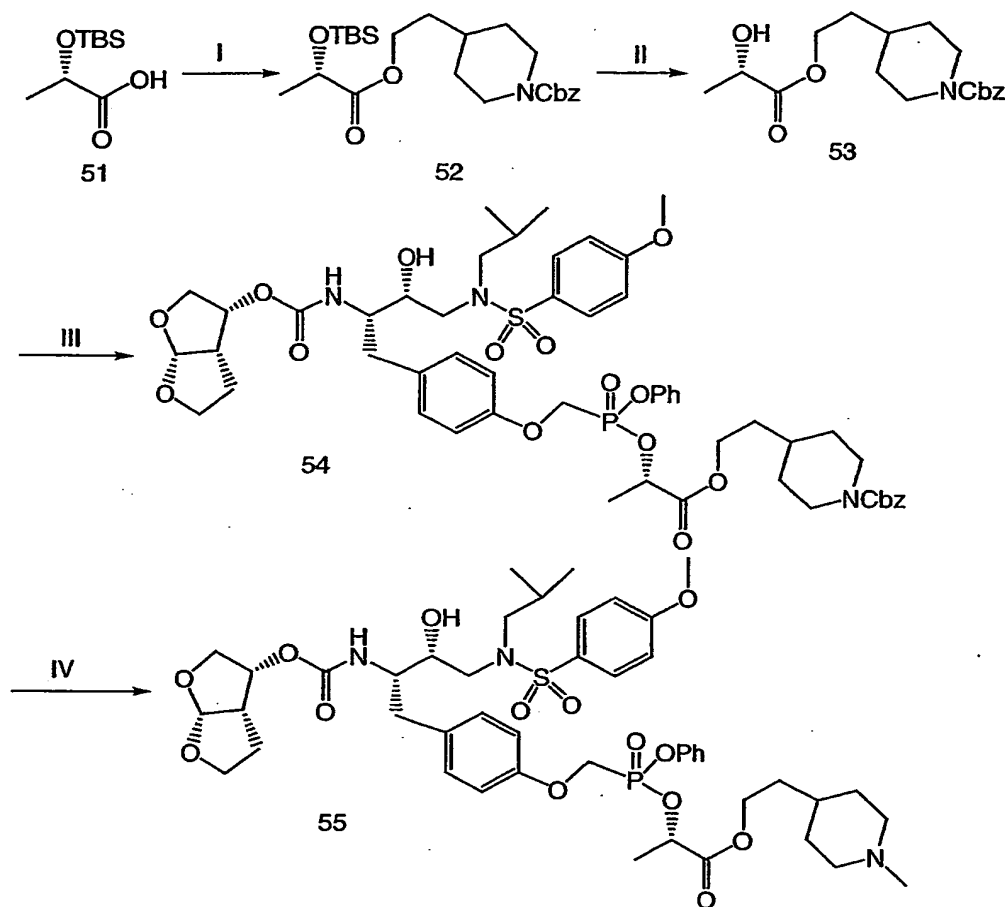
I. Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ROH/iPr₂NEt;
II.15% HF/CH₃CN; III. Compound 48/DCC/pyridine/60 C; IV. a. H₂/10%Pd-C;
b. NaBH₃CN/HCHO/HOAc

<u>Example 51</u>

Compound 51: To a solution of benzyl (s)-lactate (4.0 g, 20 mmol) in DMF (40 mL) was added imidazole (2.7 g, 20 mmol), followed by tert-butyldimethylsilyl chloride (3.3 g, 22 mmol). The mixture was stirred for 14 hours, and diluted with EtOAc. The organic phase was washed with 1.0 N HCl solution (2x), water (2x), and brine (1x), and dried over MgSO₄.

Concentration gave the lactate intermediate (6.0 g). To the solution of the above intermediate in EtOAc (200 mL) was added 10% Palladium on carbon (700 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave compound 51 (3.8 g).

5

Example 52

Compound 52: To a solution of compound 51 (1.55 g, 7.6 mmol) in CH_2Cl_2 (20 mL) was added 4-benzyloxycarbonylpiperidineethanol (2.00 g, 7.6 mmol), followed by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (4.74 g, 9.1 mmol) and

10   diisopropylethylamine (1.58 mL, 9.1 mmol). The mixture was stirred for 14 hours, and dichloromethane was removed. The mixture was diluted with EtOAc, and was washed with brine, and dried with $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 10/1) gave compound 52 (1.50 g).

15   Example 53

Compound 53: To a solution of compound 52 (1.50 g) in CH_3CN was added 58% HF/ CH_3CN (5 mL). The mixture was stirred for 30 minutes, and acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography

20   (hexanes/EtOAc = 1/1) gave compound 53 (1.00 g).

Example 54

Compound 54: To a solution of compound 48 (769 mg, 1.0 mmol) in pyridine (6.0 mL) was added compound 53 (1.0 g, 3.0 mmol), followed by DCC (618 mg, 3.0 mmol). The mixture

25   was heated at 60°C for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/4) gave compound 54 (630 mg).

Example 55

30   Compound 55: To a solution of compound 54 (630 mg, 0.58 mmol) in EtOAc (30 mL) was added 10% Palladium on carbon (63 mg), followed by acetic acid (80 μL). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave the intermediate. To the solution of the above

intermediate in EtOAc (10 mL) was added 37% formaldehyde (88 μL, 1.18 mmol), followed

by acetic acid (101 μL, 1.77 mmol). The mixture was cooled to 0°C, and sodium

cyanoborohydride (74 mg, 1.18 mmol) was added. The mixture was stirred at 25°C for 80

minutes, and was diluted with EtOAc. The mixture was washed with water and brine, and

5   was dried over MgSO$_4$. Concentration gave compound 55 as a white solid (530 mg): ^{1}H

NMR (CDCl$_3$) δ 7.74 (2 H, m), 7.40-7.15 (7 H, m), 7.03 (2 H, m), 6.92 (2 H, m), 5.66 (1 H,

m), 5.20-5.00 (3 H, m), 4.58 –4.41 (2 H, m), 4.16 (2 H, m), 4.0-3.7 (9 H, m), 3.4-2.6 (14 H,

m), 1.90-1.50 (13 H, m), 0.92 (6 H, m).

Scheme 12

57 R =

58 R =
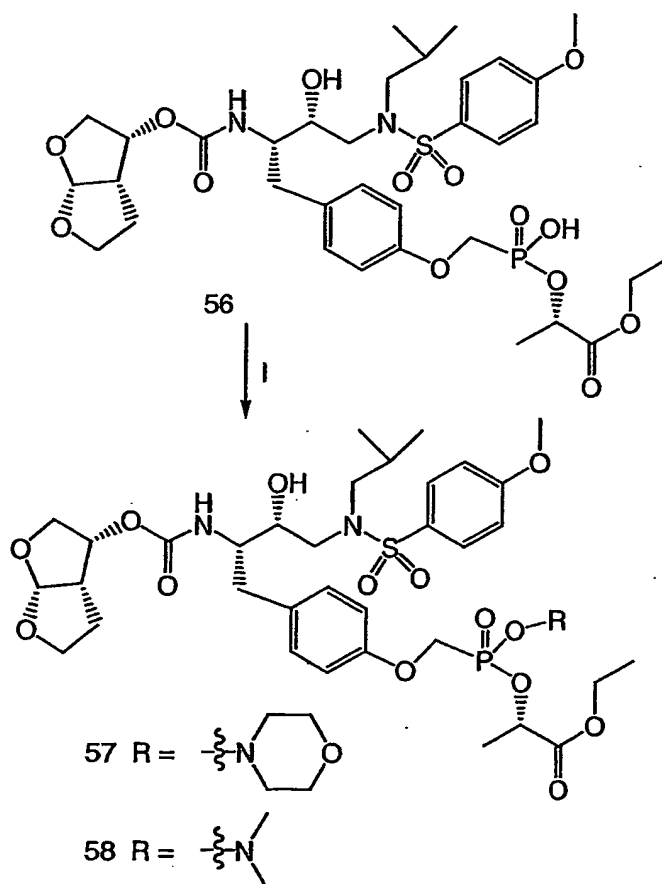
10   I. R$_2$NOH/DCC/pyridine

Example 56

Compound 56 was made by the methods of the previous Examples.

Example 57

Compound 57: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was added N-hydroxymorpholine (50 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol).

5   The mixture was stirred for 14 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography (CH$_2$Cl$_2$/iPrOH = 100/5) gave compound 57 (53 mg): ^{1}H NMR (CDCl$_3$) δ 7.71 (2 H, d, J = 8.6 Hz), 7.15 (2 H, d, J = 7.6 Hz), 6.99 (2 H, d, J = 8.8 Hz), 6.90 (2 H, m), 5.67 (1 H, m), 5.18 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.58-4.38 (2 H, m), 4.21 (2 H, m),

10 4.02-3.80 (13 H, m), 3.55-3.38 (2 H, m), 3.2-2.78 (9 H, m), 1.9-1.8 (1 H, m), 1.8-0.95 (5 H, m), 1.29 (3 H, m), 0.93 (6 H, m).

Example 58

Compound 58: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was

15 added N,N-dimethylhydroxylamine hydrochloride (47 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol). The mixture was stirred for 6 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography (CH$_2$Cl$_2$/iPrOH = 100/5) gave compound 58 (35 mg). ^{1}H NMR (CDCl$_3$) δ 7.71 (2 H, d, J = 8.9 Hz), 7.15 (2 H, d, J = 8.2 Hz), 6.99 (2 H, d, J =8.4 Hz), 6.89

20 (2 H, m), 5.65 (1 H, d, J = 5.2 Hz), 5.15 (1 H, m), 4.98 (2 H, m), 4.42 (2 H, m), 4.18 (2 H, m), 4.0-3.6 (9 H, m), 3.2-2.7 (13 H, m), 1.92-1.45 (6 H, m), 1.25 (3 H, m), 0.90 (6 H, m).

Scheme 13
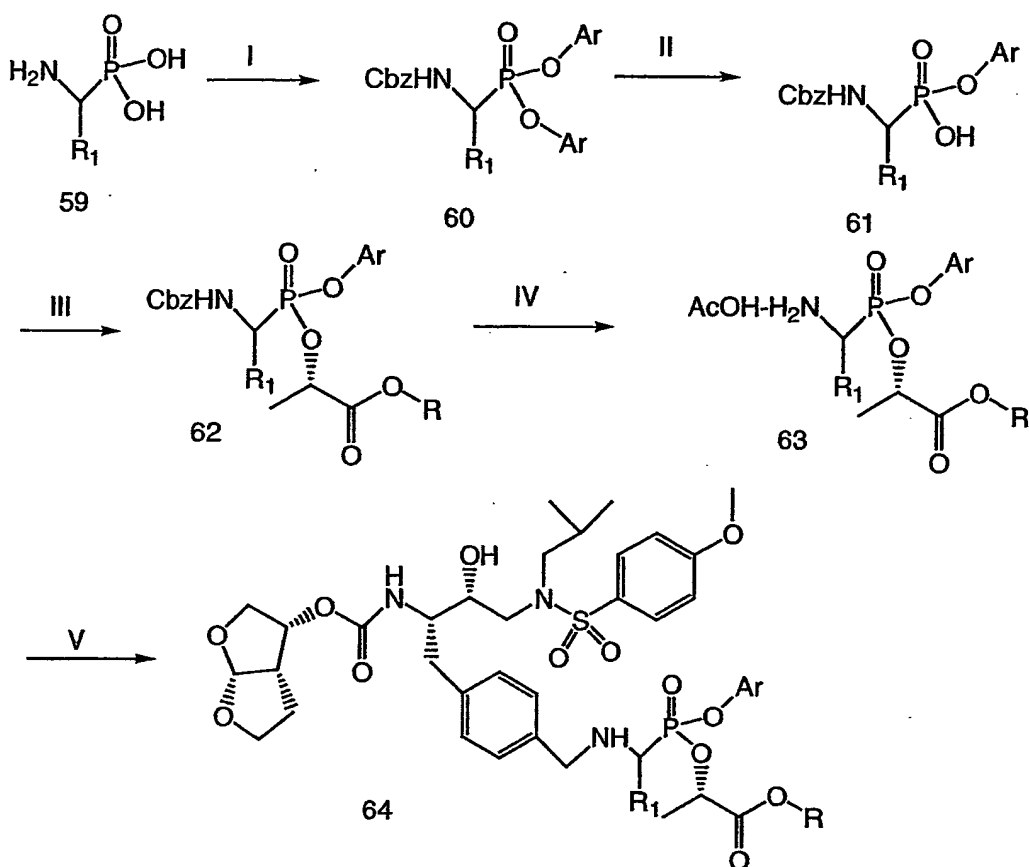
R = Me, Et, Pr, i-Pr; R₁ = H, Me, Et, i-Pr; Ar = phenyl, 2, 6-dimethylphenyl

I. a. CbzCl/NaOH; b..SOCl₂/toluene/60 C; c. ArOH/pyridine; II. a.NaOH/THF/H₂O; b. HCl;
III. a.SOCl₂/toluene/60 C; b.alkyll lactate/pyridine; IV. H₂/10%Pd-C/EtOAc/HOAc;
V. a. compound 6/MgSO₄; b. HOAc/NaCNBH₃

Aminomethylphosphonic acid 59 is protected as benzyl carbamate. The phosphonic

5   acid is treated with thionyl chloride to generate dichloridate, which reacts with phenol or 2,6-

dimethylphenol to give compound 60. Compound 60 is hydrolyzed with sodium hydroxide,

followed by acidification to afford monoacid 61. Monoacid 61 is treated with thionyl

chloride to generate monochloridate, which reacts with different alkyl (s)-lactates to form

compound 62. Compound 62 is hydrogenated with 10%Pd-C in the presence of acetic acid to

give compound 63. Compound 63 reacts with aldehyde 6 in the presence of $MgSO_4$ to form

imine, which is reduced with sodium cyanoborohydride to generate compound 64.

Scheme 14
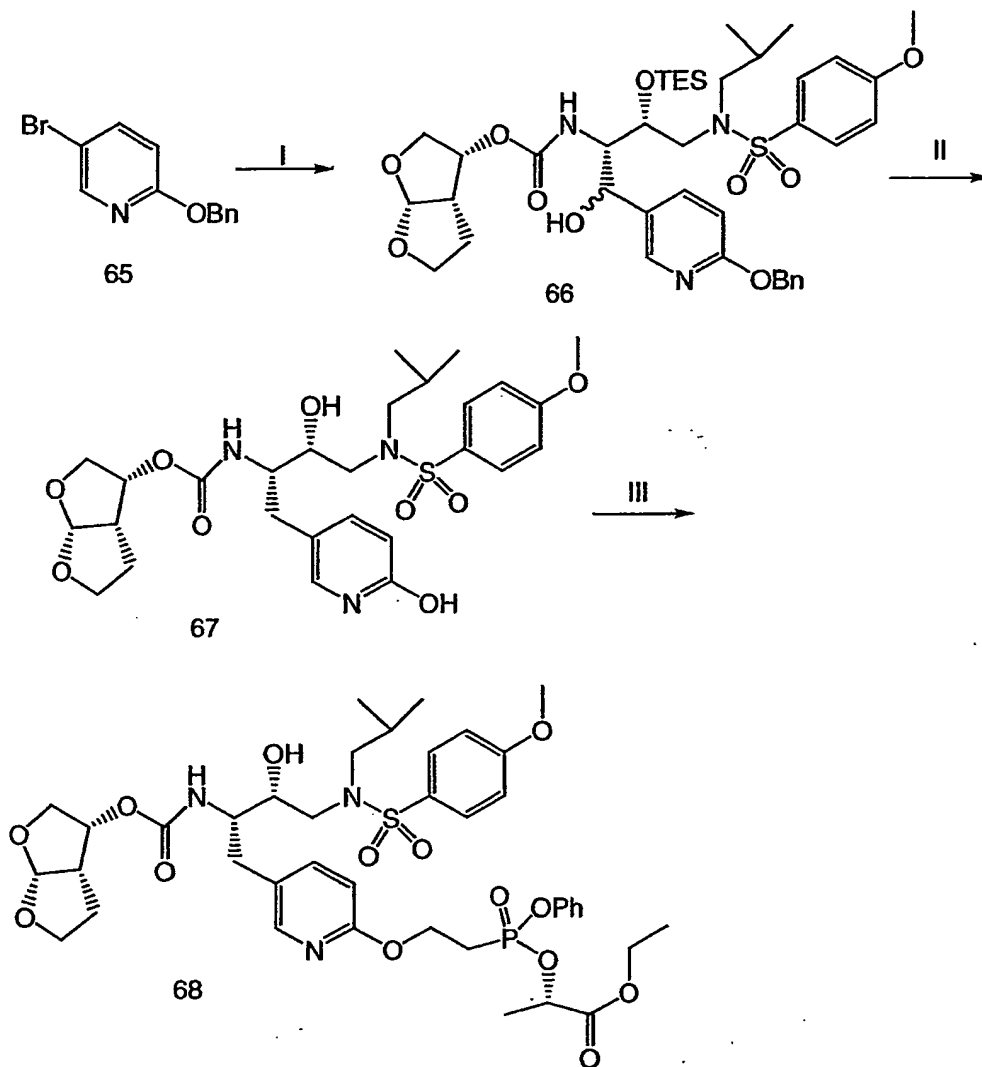
I.a. n-BuLi; b. compound 15; II. H_2/10%Pd-C/HOAc; IV. PPh_3/DEAD

Compound 65 is prepared from 2-hydroxy-5-bromopyridine by alkylation. J. Med.

5   Chem. 1992, 35, 3525. Compound 65 is treated with n-Butyl lithium to generate aryl lithium,

which reacts with aldehyde 15 to form compound 66. J. Med. Chem. 1994, 37, 3492.

Compound 66 is hydrogenated with 10%Pd-C in the presence of acetic acid to give

compound 67. J. Med. Chem. 2000, 43, 721. Compound 68 is prepared from compound 67

with corresponding alcohol under Mitsunobu reaction conditions. Bioorg. Med.Chem. Lett.. 1999, 9, 2747.

Scheme 1
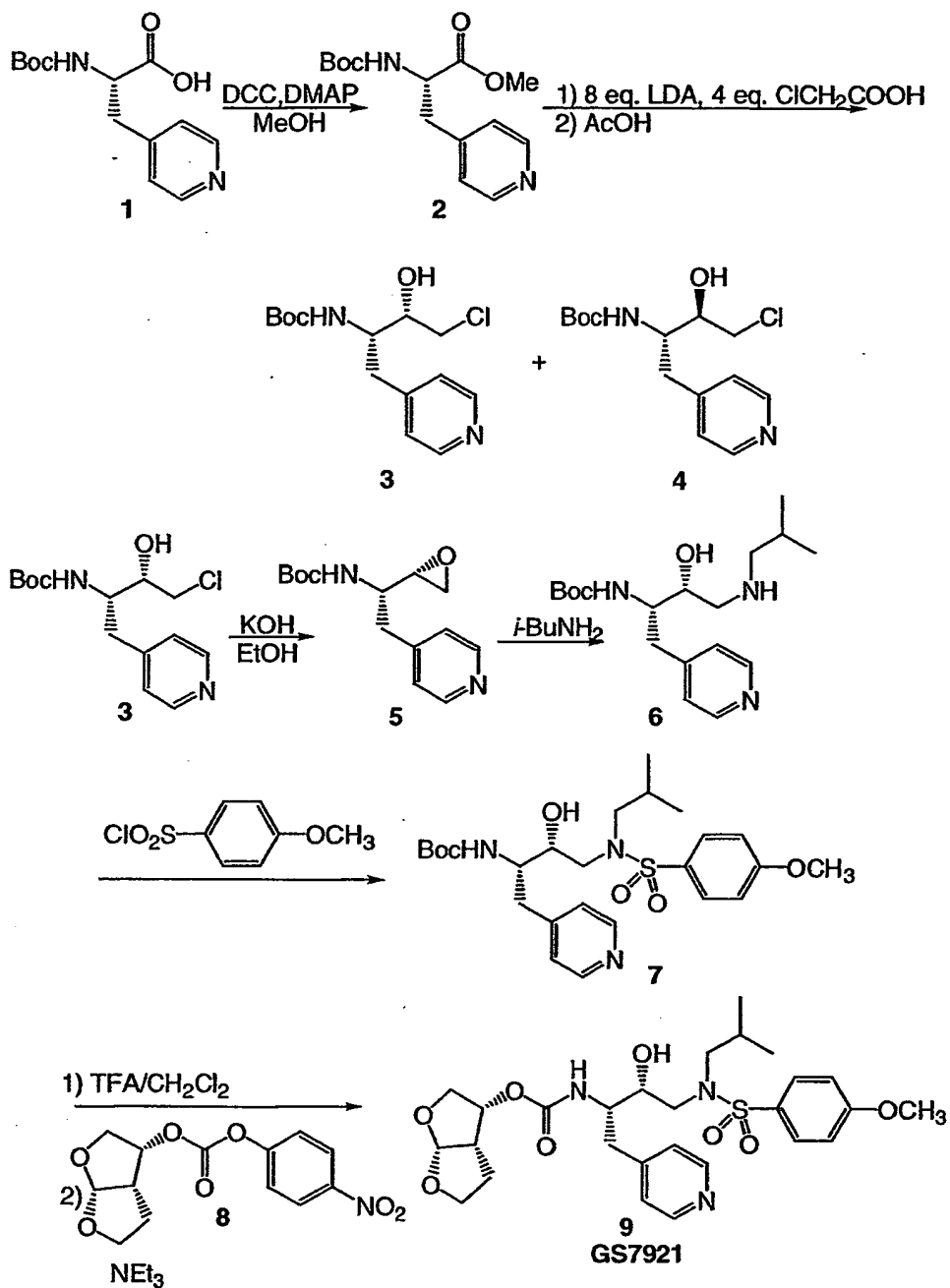
Example 1

Methyl 2-(S)-(dimethylethoxycarbonylamino)-3-(4-pyridyl)propanoate (2): A solution of N-tert-Butoxycarbonyl-4-pyridylalanine (1, 9.854 g, 37 mmol, Peptech), 4-dimethylaminopyridine (4.52 g, 37 mmol, Aldrich), and dicyclohexylcarbodiimide (15.30 g,

5   74.2 mmol, Aldrich) in methanol (300 mL) was stirred at 0°C for 2 h and at room temperature for 12 h. After the solids were removed by filtration, the filtrate was concentrated under reduced pressure. More dicyclohexylurea was removed by repeated trituration of the concentrated residue in EtOAc followed by filtration. The residue was chromatographed on silica gel to afford the methyl ester 2 (9.088 g, 88%): ^{1}H NMR (CDCl$_3$)

10   δ 8.53 (d, 2H, J = 5.7 Hz), 7.09 (d, 2H, J = 5.7 Hz), 5.04 (br, 1H), 4.64 (br, 1H), 3.74 (s, 3H), 3.16 (dd, 1H, J = 13.5 and 5.7 Hz), 3.02 (dd, 1H, J = 13.5 and 6.3 Hz), 1.42 (s, 9H); MS (ESI) 281 (M+H).

Example 2

1-Chloro-3-(S)-(dimethylethoxycarbonylamino)-4-(4-pyridyl)-2-(S)-butanol (3): A solution

15   of diisopropylamine (37.3 mL, 266 mmol, Aldrich) in THF (135 mL) was stirred at –78°C as a solution of n-butyllithium (102 mL of 2.3 M solution and 18 mL of 1.4 M solution 260 mmol, Aldrich) in hexane was added. After 10 min, the cold bath was removed and stirred the solution for 10 min at the ambient temperature. The solution was cooled at –78°C again and stirred as a solution of chloroacetic acid (12.255 g, 130 mmol, Aldrich) in THF (50 mL)

20   was added over 20 min. After the solution was stirred for 15 min, this dianion solution was transferred to a stirred solution of the methyl ester 2 (9.087 g, 32.4 mmol) in THF (100 mL) at 0°C over 15 min. The resulting yellow slurry was stirred at 0°C for 10 min and cooled at – 78°C. A solution of acetic acid (29 mL, 507 mmol, Aldrich) in THF (29 mL) was added quickly to the slurry and the resulting slurry was stirred at –78°C for 30 min, at 0°C for 30

25   min, and at room temperature for 15 min. The resulting slurry was dissolved in saturated NaHCO$_3$ solution (750 mL) and EtOAc (500 mL). The separated aqueous layer was extracted with EtOAc (300 mL x 2) and the combined organic fractions were washed with water (750 mL x 2) and saturated NaCl solution (250 mL). The resulting solution was dried (MgSO$_4$) and evaporated under reduced pressure.

30   A solution of the residue in THF (170 mL) and water (19 mL) was stirred at 0°C as NaBH$_4$ (3.375 g, 89.2 mmol, Aldrich) was added. After 30 min, the solution was evaporated under reduced pressure and the residue was dissolved in EtOAc, acidified with aqueous NaHSO$_4$,

and then neutralized by adding saturated aqueous NaHCO₃ solution. The separated aqueous
fraction was extracted with EtOAc (100 mL) and the combined organic fractions were
washed with water (500 mL) and saturated NaCl solution (100 mL). The solution was dried
(MgSO₄) and evaporated under reduced pressure. The residue was chromatographed on

5   silica gel to afford the chlorohydrin 3 and 4 (4.587 g, 47%) as a mixture of two diastereomers
(3~4:1). The obtained mixture was recrystallized from EtOAc-hexane twice to obtain pure
desired diastereomer 3 (2.444 g, 25%) as yellow crystals: ^{1}H NMR (CDCl₃) δ 8.53 (d, 2H, J
= 5.7 Hz), 7.18 (d, 2H, J = 5.7 Hz), 4.58 (br, 1H), 3.94 (m, 1H), 3.87 (br, 1H), 3.75-3.54 (m,
2H), 3.05 (dd, 1H, J = 13.8 and 3.9 Hz), 2.90 (dd, 1H, J = 13.8 and 8.4 Hz), 1.36 (s, 9H); MS

10   (ESI) 301 (M+H).

Example 3

The epoxide 5: A solution of the chlorohydrin 3 (1.171 g, 3.89 mmol) in ethanol (39 mL)
was stirred at room temperature as 0.71 M KOH in ethanol (6.6 mL) was added. After 1.5 h,
the mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc

15   (60 mL) and water (60 mL). The separated aqueous fraction was extracted with EtOAc (60
mL) and the combined organic fractions were washed with saturated NaCl solution, dried
(MgSO₄), and concentrated under reduced pressure to obtain the epoxide (1.058 g,
quantitative): ^{1}H NMR (CDCl₃) δ 8.52 (d, 2H, J = 6.0 Hz), 7.16 (d, 2H, J = 6.0 Hz), 4.57 (d,
1H, J = 7.8 Hz), 3.76 (br, 1H), 3.02-2.92 (m, 2H), 2.85-2.79 (m, 2H), 2.78-2.73 (m, 1H), 1.37

20   (s, 9H); MS (ESI) 265 (M+H).

Example 4

The hydroxy-amine 6: A solution of the epoxide 5 obtained above and i-BuNH₂ (3.9 mL,
39.2 mmol, Aldrich) in 58 mL of i-PrOH was stirred at 65°C for 2 h and the solution was
concentrated under reduced pressure. The residual i-PrOH was removed by dissolving the

25   residue in toluene and concentration of the solution twice: ^{1}H NMR (CDCl₃) δ 8.51 (d, 2H, J
= 6.0 Hz), 7.18 (d, 2H, J = 6.0 Hz), 4.70 (d, 1H, J = 9.6 Hz), 3.86 (br, 1H), 3.46 (q, 1H, J =
5.8 Hz), 3.06 (dd, 1H, J = 14.1 and 3.9 Hz), 2.79 (dd, 1H, J = 14.1 and 9.0 Hz), 2.76-2.63 (m,
3H), 2.43 (m, 2H, J = 6.9 Hz), 1.73 (m, 1H, J = 6.6 Hz), 1.36 (s, 9H), 0.93 (d, 3H, J = 6.6
Hz), 0.92 (d, 3H, J = 6.6 Hz); MS (ESI) 338 (M+H).

Example 5

The sulfoamide 7: A solution of the crude 6 and p-methoxybenzene sulfonyl chloride (890 mg, 4.31 mmol, Aldrich) in CH_2Cl_2 (24 mL) was stirred at 0°C for 2 h and at room temperature for 13 h. The solution was washed with saturated $NaHCO_3$ solution and the aqueous washing was extracted with CH_2Cl_2 (60 mL). After the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to obtain the sulfoamide 7 (1.484 g, 75%): ^1H NMR ($CDCl_3$) δ 8.51 (d, 2H, $J = 5.7$ Hz), 7.73 (d, 2H, $J = 8.7$ Hz), 7.21 (d, 2H, $J = 5.7$ Hz), 7.00 (d, 2H, $J = 8.7$ Hz), 4.68 (d, 1H, $J = 8.1$ Hz), 4.08 (br, 1H), 3.88 (s, 3H), 3.83 (br, 2H), 3.09 (d, 2H, $J = 5.1$ Hz), 3.06-2.80 (m, 4H), 1.85 (m, 1H, $J = 7.0$ Hz), 1.34 (s, 9H), 0.92 (d, 3H, $J = 6.3$ Hz), 0.89 (d, 3H, $J = 6.6$ Hz); MS (ESI) 508 (M+H).

Example 6

The bisfurancarbamate 9: A solution of the sulfoamide 7 (1.484 g, 2.92 mmol) and trifluoroacetic acid (6.8 mL, 88.3 mmol, Aldrich) in CH_2Cl_2 (18 mL) was stirred at room temperature for 2 h. After the solution was evaporated under reduced pressure, the residue was dissolved in acetonitrile (10 mL) and toluene (10 mL), and evaporated to dryness twice to result crude amine as TFA salt. A solution of the crude amine, dimethylaminopyridine (72 mg, 0.59 mmol, Aldrich), diisopropylethylamine (2.55 mL, 14.6 mmol, Aldrich) in acetonitrile was stirred at 0°C as the bisfurancarbonate 8 (907 mg, 3.07 mmol, obtained from Azar) was added in portion. The solution was stirred at 0°C for 1 h and at room temperature for 19 h, and concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and washed with saturated $NaHCO_3$ solution (60 mL). After the aqueous washing was extracted with EtOAc (60 mL), the combined organic fractions were washed with saturated $NaHCO_3$ (60 mL) and saturated NaCl solution (60 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the carbamate 9 (1.452 g, 88%): ^1H NMR ($CDCl_3$) δ 8.50 (d, 2H, $J = 5.7$ Hz), 7.72 (d, 2H, $J = 8.7$ Hz), 7.19 (d, 2H, $J = 5.7$ Hz), 7.01 (d, 2H, $J = 8.7$ Hz), 5.65 (d, 1H, $J = 5.1$ Hz), 5.12 (d, 1H, $J = 9.3$ Hz), 5.02 (q, 1H, $J = 6.7$ Hz), 4.01-3.77 (m, 4H), 3.88 (s, 3H), 3.76-3.63 (m, 2H), 3.18-2.76 (m, 7H), 1.95-1.77 (m, 1H), 1.77-1.56 (m, 2H), 1.56-1.41 (m, 1H), 0.94 (d, 3H, $J = 6.6$ Hz), 0.90 (d, 3H, $J = 6.9$ Hz); MS (ESI) 564 (M+H).

Scheme 2
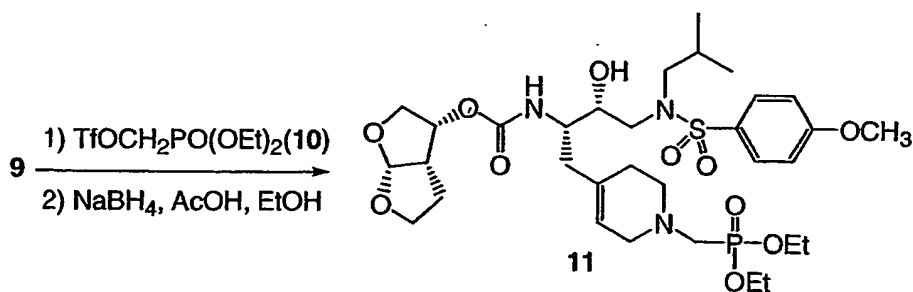
GS192710

Example 7

The tetrahydropyridine-diethyl phosphonate 11: A solution of the pyridine 9 (10.4 mg, 0.018 mmol) and the triflate 10 (8.1 mg, 0.027 mmol, in acetone-d_6 (0.75 mL) was stored at room temperature for 9 h and the solution was concentrated under reduced pressure: ^{31}P NMR (acetone-d_3) δ 14.7; MS (ESI) 714 (M$^+$). The concentrated crude pyridinium salt was dissolved in ethanol (2 mL) and stirred at room temperature as NaBH$_4$ (~10 mg, Aldrich) was added occasionally over 4 h. To the mixture was added a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL) until the pH of the mixture became 3~4. More NaBH$_4$ and acetic acid were added until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was dissolved in saturated NaHCO3 solution (10 mL). The product was extracted using EtOAc (10 mL x 3) and washed with saturated NaCl solution, dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the product 11 (8.5 mg, 64%): ^{1}H NMR (CDCl$_3$) δ 7.73 (d, 2H, J = 8.7 Hz), 7.00 (d, 2H, J = 8.7 Hz), 5.71 (d, 1H, J = 5.1 Hz), 5.41 (br, 1H), 5.15-5.08 (m, 1H), 5.00 (br, 1H), 4.14 (dq, 4H, J = 7.2 Hz), 4.06-3.94 (m, 2H), 3.88 (s, 3H), 3.92-3.80 (m, 2H), 3.75 (dd, 1H, J = 9.6 and 6.6 Hz), 3.79-3.61 (m, 1H), 3.24-2.94 (m, 6H), 2.85 (d, 2H, J = 11.7 Hz), 2.88-2.76 (m, 2H), 2.75-2.63 (m, 1H), 2.38-2.29 (m, 1H), 2.24-2.2.12 (m, 2H), 2.12-1.78 (m, 4H), 1.30 (t, 6H, J = 7.1 Hz), 0.94 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.3 Hz); ^{31}P NMR (CDCl$_3$) δ 24.6; MS (ESI) 740 (M+Na).

Scheme 3
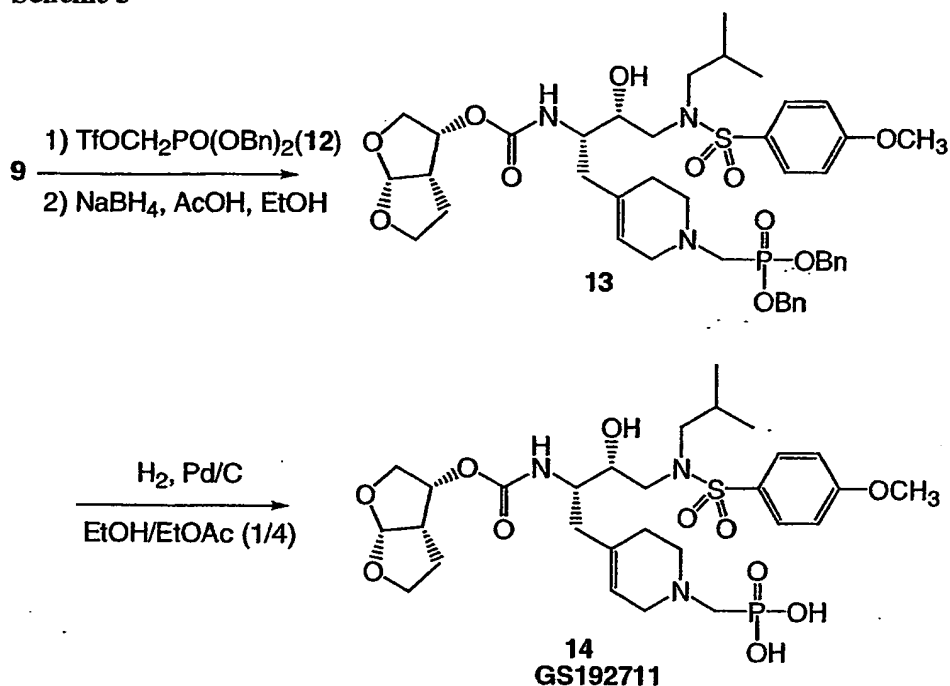
Example 8

The tetrahydropyridine-dibenzyl phosphonate 13: The compound 13 was obtained by the same procedure as described for compound 11 using the pyridine 9 (10.0 mg, 0.018 mmol) and the triflate 12 (9.4 mg, 0.022 mmol). The product 13 was purified by preparative TLC to afford the dibenzyl phosphonate 13 (8.8 mg, 59%): ^{1}H NMR (CDCl$_3$) δ 7.73 (d, 2H, J = 8.7 Hz), 7.35 (s, 10H), 7.00 (d, 2H, J = 8.7 Hz), 5.65 (d, 1H2H, J = 5.1 Hz), 5.39 (br, 1H), 5.15-4.92 (m, 6H), 4.03-3.77 (m, 6H), 3.77-3.62 (m, 2H), 3.56 (br, 1H), 3.24-2.62 (m, 9H), 2.32 (d, 1H, J = 13.5 Hz), 2.24-1.75 (m, 6H), 0.94 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.3 Hz); ^{31}P NMR (CDCl$_3$) δ 25.5; MS (ESI) 842 (M+H).

Example 9

The phosphonic acid 14: A mixture of the dibenzyl phosphonate 13 (8.8 mg, 0.011 mmol) and 10% Pd/C in EtOAc (2 mL) and EtOH (0.5 mL) was stirred under H$_2$ atmosphere for 10 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford the product 14 (6.7 mg, quantitative): ^{1}H NMR (CD$_3$OD) δ 7.76 (d, 2H, J = 9.0 Hz), 7.10 (d, 2H, J = 9.0 Hz), 5.68 (d, 1H, J = 5.1 Hz), 5.49 (br, 1H), 5.11 (m, 1H), 3.90 (s, 3H), 4.04-3.38 (m, 10H), 3.22 (d, 2H, J = 12.9 Hz), 3.18-3.00 (m, 2H),

2.89-2.75 (m, 2H), 2.68-2.30 (m, 3H), 2.21-1.80 (m, 4H), 0.92 (d, 3H, J = 6.3 Hz), 0.85 (d, 3H, J = 6.3 Hz); ^{31}P NMR (CD$_3$OD) δ 6.29; MS (ESI) 662 (M+H).

Scheme 4
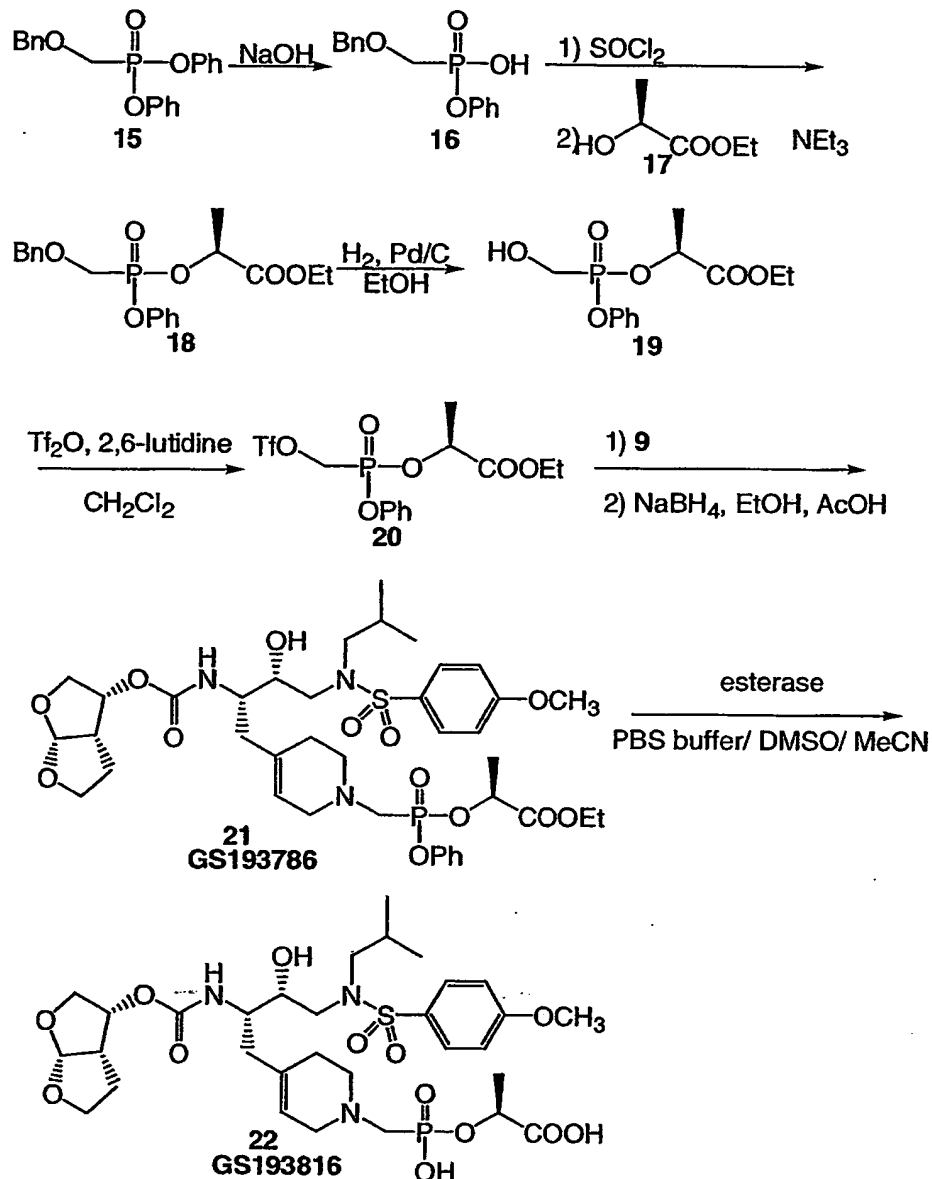
Example 10

Diphenyl benzyloxymethylphosphonate 15: To a solution of diphenylphosphite (46.8 g, 200 mmol, Aldrich) in acetonitrile (400 mL) (at ambient temperature) was added potassium carbonate (55.2 g, 400 mmol) followed by the slow addition of benzyl chloromethyl ether (42

mL, 300 mmol, about 60%, Fluka). The mixture was stirred overnight, and was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, saturated NaCl, dried (Na$_2$SO$_4$), filtered and evaporated. The crude product was chromatographed on silica gel to afford the benzylether (6.8 g, 9.6%) as a colorless liquid.

5

Example 11

Monoacid 16: To a solution of diphenyl benzyloxymethylphosphonate 15 (6.8 g, 19.1 mmol) in THF (100 mL) at room temperature was added 1N NaOH in water (21 mL, 21 mmol). The

10   solution was stirred 3 h. The THF was evaporated under reduced pressure and water (100 mL) was added. The aqueous solution was cooled to 0°C, neutralized to pH 7 with 3N HCl and washed with EtOAc. The aqueous solution was again cooled to 0°C, acidified with 3N HCl to pH 1, saturated with sodium chloride, and extracted with EtOAc. The organic layer was washed with brine and dried (Na$_2$SO$_4$), filtered and evaporated, then co-evaporated with

15   toluene to yield the monoacid (4.0 g, 75%) as a colorless liquid. ^{1}H NMR (CDCl$_3$) δ 7.28-7.09 (m, 10H), 4.61 (s, 2H), 3.81 (d, 2H);. ^{31}P NMR (CDCl$_3$) δ 20.8.

Example 12

20   Ethyl lactate phosphonate 18: To a solution of monoacid 16 (2.18 g, 7.86 mmol) in anhydrous acetonitrile (50 mL) under a nitrogen atmosphere was slowly added thionyl chloride (5.7 mL, 78mmol). The solution was stirred in a 70°C oil bath for three hours, cooled to room temperature and concentrated. The residue was dissolved in anhydrous dichloromethane (50mL), and this solution cooled to 0°C and stirred under a nitrogen atmosphere. To the

25   stirring solution was added ethyl (S)-(-)-lactate (2.66 mL, 23.5 mmol) and triethylamine (4.28 mL, 31.4 mmol). The solution was warmed to room temperature and allowed to stir for one hour. The solution was diluted with ethyl acetate, washed with water, brine, citric acid and brine again, dried (MgSO$_4$), filtered through Celite, concentrated under reduced pressure and chromatographed on silica gel using 30% ethylacetate in hexane. The two diastereomers

30   were pooled together. ^{1}H NMR (CDCl$_3$) δ 7.40-7.16 (m, 20H), 5.18-5.13 (m, 2H), 4.73 (s, 2H), 4.66 (d, 2H), 4.28-4.11 (m, 5H), 4.05 (d, 2H), 3.95 (d, 2H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.18 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 19.6, 17.7.

Example 13

Ethyl lactate phosphonate with free alcohol 19: Ethyl lactate phosphonate 18 was dissolved in EtOH (50mL) and under a nitrogen atmosphere 10% Pd-C (approximately 20 wt %) was

5   added. The nitrogen atmosphere was replaced with hydrogen (1atm) and the suspension stirred for two hours. 10% Pd-C was again added (20 wt %) and the suspension stirred five hours longer. Celite was added, the reaction mixture was filtered through Celite and the filtrate was concentrated to afford 1.61 g (71% from monoacid 16) of the alcohol as a colorless liquid. ^{1}H NMR (CDCl$_3$) δ 7.40-7.16 (m, 10H), 5.16-5.03 (m, 2H), 4.36-4.00 (m,

10   8H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.22 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 22.3, 20.0.

Example 14

Triflate 20: To a solution of ethyl lactate phosphonate with free alcohol 19 (800 mg, 2.79

15   mmol) in anhydrous dichloromethane (45 mL) chilled to -40°C under a nitrogen atmosphere was added triflic anhydride (0.516 mL, 3.07 mmol) and 2-6 lutidine (0.390 mL, 3.34 mmol). The solution was stirred for 3 hr, then warmed to -20°C and stirred one hour longer. 0.1 equivalents of triflic anhydride and 2-6 lutidine were then added and stirring was resumed for 90 minutes more. The reaction mixture was diluted with ice-cold dichloromethane, washed

20   with ice-cold water, washed with ice-cold brine and the organic layer was dried (MgSO$_4$) and filtered. The filtrate was concentrated and chromatographed on silica gel using 30% EtOAc in hexane as eluent to afford 602 mg (51%) of the triflate diastereomers as a slightly pink, transparent liquid. ^{1}H NMR (CDCl$_3$) δ 7.45-7.31 (m, 4H), 7.31-7.19 (m, 6H), 5.15-4.75 (m, 6H), 4.32-4.10 (4H), 1.62 (d, 3H), 1.50 (d, 3H), 1.30-1.22 (m, 6H); ^{31}P NMR (CDCl$_3$)

25   δ 10.3, 8.3.

Example 15

The tetrahydropyridine-prodrug 21: A solution of the pyridine 9 (11.1 mg, 0.020 mmol) and

30   the triflate 20 (11.4 mg, 0.027 mmol) in acetone-d$_6$ (0.67 mL, Aldrich) was stored at room temperature for 7 h and the solution was concentrated under reduced pressure: ^{31}P NMR (acetone-d$_6$) δ 11.7, 10.9; MS (ESI) 838 (M+H). The concentrated crude pyridinium salt was dissolved in ethanol (1 mL) and added 2~3 drops of a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL). The solution was stirred at 0°C as NaBH$_4$ (7~8 mg, Aldrich) was

added. More acetic acid solution was added to adjust pH 3~4 of the reaction mixture. Additions of NaBH₄ and the acetic acid solution were repeated until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was purified by chromatography on C18 reverse phase column material followed by

5 preparative TLC using C18 reverse phase plate to obtain the prodrug 21 (13.6 mg, 70%) as a 2:3 mixture of two diastereomers: ^{1}H NMR (CD₃CN) δ 7.78 (d, 2H, J = 9.0 Hz), 7.48-7.42 (m, 2H), 7.35-7.27 (m, 3H), 7.10 (d, 2H, J = 9.0 Hz), 5.86 (m, 1H), 5.60 (m, 1H), 5.48 (br, 1H), 5.14-5.03 (m, 2H), 4.29-4.13 (m, 2H), 3.89 (s, 3H), 3.97-3.32 (m, 12H), 3.29 (br, 0.4H), 3.24 (br, 0.6H), 3.02-2.82 (m, 4H), 2.64-2.26 (m, 3H), 2.26-2.08 (m, 1H), 1.94-1.76 (m, 3H),

10 1.57 (d, 1.8H, J = 6.9 Hz), 1.46 (d, 1.2H, J = 6.9 Hz), 1.28 (d, 1.2H, J = 6.9 Hz), 1.21 (d, 1.8H, J = 7.2 Hz), 0.92-0.88 (m, 6H); ^{31}P NMR (CD₃CN) δ 14.4 (0.4P), 13.7 (0.6P); MS (ESI) 838 (M+H).

Example 16

15

Metabolite 22: To a solution of the prodrug 21 (10.3 mg, 0.011 mmol) in DMSO (0.1 mL) and acetonitrile (0.2 mL) was added 0.1 M PBS buffer (3 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.05 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 1.5 h, the mixture was

20 centrifuged and the supernatant was taken. The product was purified by HPLC and the collected fraction was lyophilized to result the product 22 as trifluoroacetic acid salt (7.9 mg, 86%): ^{1}H NMR (D₂O) δ 7.70 (d, 1H), 7.05 (d, 2H), 5.66 (d, 1H), 5.40 (br, 1H), 5.02 (br, 1H), 4.70 (br, 1H), 3.99-3.89 (m, 2H), 3.81 (s, 3H), 3.83-3.50 (m, 8H), 3.34-2.80 (m, 7H), 2.50-2.18 (m, 3H), 2.03 (m, 1H), 1.92-1.70 (m, 3H), 1.39 (d, 3H), 0.94 (d, 3H), 0.93 (d, 3H);

25 ^{31}P NMR (D₂O) δ 9.0, 8.8; MS (ESI) 734 (M+H).

Scheme 5

25
GS273819
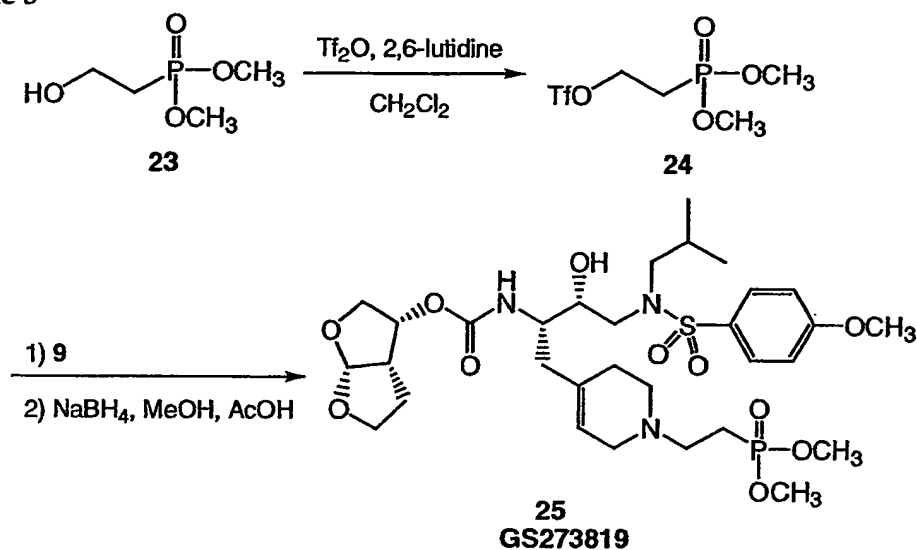
Example 17

Triflate 24: Triflate **24** was prepared analogously to triflate **20**, except that dimethylhydroxyethylphosphonate **23** (Aldrich) was substituted for ethyl lactate phosphonate with free alcohol **19**.

Example 18

Tetrahydropyridine 25: Tetrahydropyridine **25** was prepared analogously to tetrahydropyridine **30**, except that triflate **24** was substituted for triflate **29**.

^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.01 (d, 2H), 5.71 (d, 2H), 5.43 (bs, 1H), 5.07-4.87 (m, 1H), 4.16-3.46 (m, 13H), 3.34-3.18 (m, 3H), 3.16-2.80 (m, 5H), 2.52-1.80 (m, 12H), 1.28-1.04 (m, 3H+H$_2$O peak), 0.98-0.68 (m, 6H).

Scheme 6
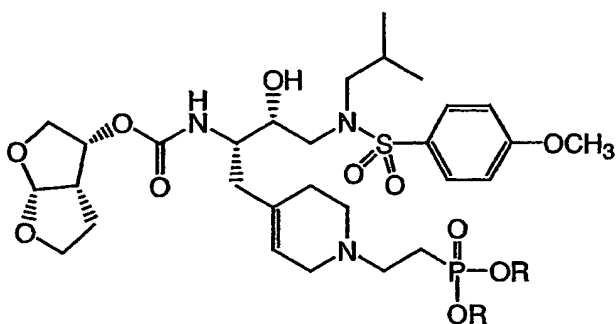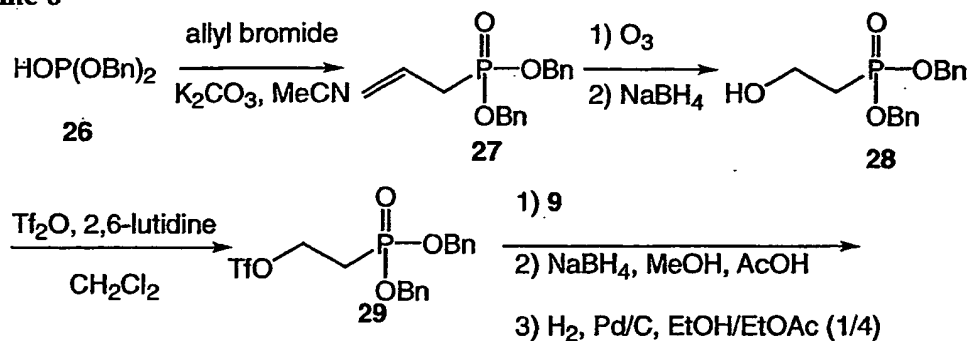
30: R = Bn (GS173848)
31: R = H (GS173850)

5   **Example 19**

Dibenzyl phosphonate with double bond 27: To a stirring solution of allyl bromide (4.15 g, 34 mmol, Aldrich) and dibenzylphosphite (6 g, 23 mmol, Aldrich) in acetonitrile (25 mL) was added potassium carbonate (6.3 g, 46 mmol, powder 325 mesh Aldrich) to create a suspension, which was heated to 65°C and stirred for 72 hours. The suspension was cooled

10   to room temperature, diluted with ethyl acetate, filtered, and the filtrate was washed with water, then brine, dried (MgSO₄), concentrated and used directly in the next step.

Example 20

Dibenzylhydroxyethylphosphonate 28: Dibenzyl phosphonate with double bond 27 was

15   dissolved in methanol (50mL), chilled to -78°C, stirred, and subjected to ozone by bubbling ozone into the solution for three hours until the solution turned pale blue. The ozone flow was stopped and oxygen bubbling was done for 15 minutes until the solution became colorless. Sodium borohydride (5 g, excess) was added slowly portionwise. After the evolution of gas subsided the solution was allowed to warm to room temperature,

20   concentrated, diluted with ethyl acetate, made acidic with acetic acid and water and

partitioned. The ethyl acetate layer was washed with water, then brine and dried (MgSO₄), filtered, concentrated and chromatographed on silica gel eluting with a gradient of eluent from 50% ethyl acetate in hexane to 100% ethyl acetate, affording 2.76 g of the desired product. ^{1}H NMR (CDCl₃) δ 7.36 (m, 10H), 5.16-4.95 (m, 4H), 3.94-3.80 (dt, 2H), 2.13-2.01

5   (dt, 2H); ^{31}P NMR (CDCl₃) δ 31.6.

Example 21

Dibenzyl phosphonate 30: A solution of the alcohol 28 (53.3 mg, 0.174 mmol) and 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich) in CH₂Cl₂ (1 mL) was stirred at –45°C as

10   trifluoromethanesulfonic anhydride (0.029 mL, 0.172 mmol, Aldrich) was added. The solution was stirred for 1 h at –45°C and evaporated under reduced pressure to obtain the crude triflate 29.

A solution of the crude triflate 29, 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich), and the pyridine 9 in acetone-d₆ (1.5 mL, Aldrich) was stored at room temperature for 2 h. The

15   solution was concentrated under reduced pressure to obtain crude pyridinium product: ^{31}P NMR (acetone-d₆) δ 25.8; MS (ESI) 852 (M⁺).

To a solution of the crude pyridinium salt in ethanol (2 mL) was added 7~8 drops of a solution of acetic acid (0.4 mL, Aldrich) in ethanol (2 mL). The solution was stirred at 0°C as NaBH₄ (7~8 mg) was added. The solution was maintained to be pH 3-4 by adding the

20   acetic acid solution. More NaBH₄ and the acetic acid were added until the reduction was completed. After 4 h, the mixture was concentrated and the remaining residue was dissolved in saturated NaHCO₃ (10 mL). The product was extracted with EtOAc (10 mL x 3), dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by repeated chromatography on silica gel followed by HPLC purification. Lyophilization of the collected

25   fraction resulted the product 30 (13.5 mg, 26%) as trifluoroacetic acid salt: ^{1}H NMR (CDCl₃) δ 7.72 (d, 2H, J = 8.7 Hz), 7.36 (br, 10H), 7.00 (d, 2H, J = 8.7 Hz), 5.69 (d, 1H, J = 5.1 Hz), 5.41 (br, 1H), 5.13-4.93 (m, 6H), 4.05-2.5 (m, 19H), 3.88 (s, 3H), 2.5-1.9 (m, 5H), 1.90-1.74 (m, 2H), 0.88 (d, 6H, J = 6.1 Hz); ^{31}P NMR (CDCl₃) δ 25.8; MS (ESI) 856 (M+H).

30   Example 22

Phosphonic acid 31: A mixture of the dibenzyl phosphonate 30 (9.0 mg, 0.009 mmol) and 10% Pd/C (5.2 mg, Aldrich) in EtOAc (2 mL) and ethanol (0.5 mL) was stirred under H₂ atmosphere for 3 h at room temperature. After the mixture was filtered through celite, a drop

of trifluoroacetic acid (Aldrich) was added to the filtrate and the filtrate was concentrated to dryness to afford the product **31** (6.3 mg, 86%): ^{1}H NMR (CD$_3$OD) δ 7.76 (d, 2H, J = 9.0 Hz), 7.11 (d, 2H, J = 9.0 Hz), 5.69 (d, 1H, J = 5.1 Hz), 5.54 (br, 1H), 5.09 (br, 1H), 4.05-3.84 (m, 4H), 3.89 (s, 3H), 3.84-3.38 (m, 9H), 3.07 (dd, 2H, J = 13.5 and 8.4 Hz), 2.9-2.31 (m,

5   5H), 2.31-1.83 (m, 6H), 0.92 (d, 3H, J = 6.3 Hz), 0.85 (d, 3H, J = 6.9 Hz); ^{31}P NMR (CD$_3$OD) δ 21.6; MS (ESI) 676 (M+H).

Scheme 7
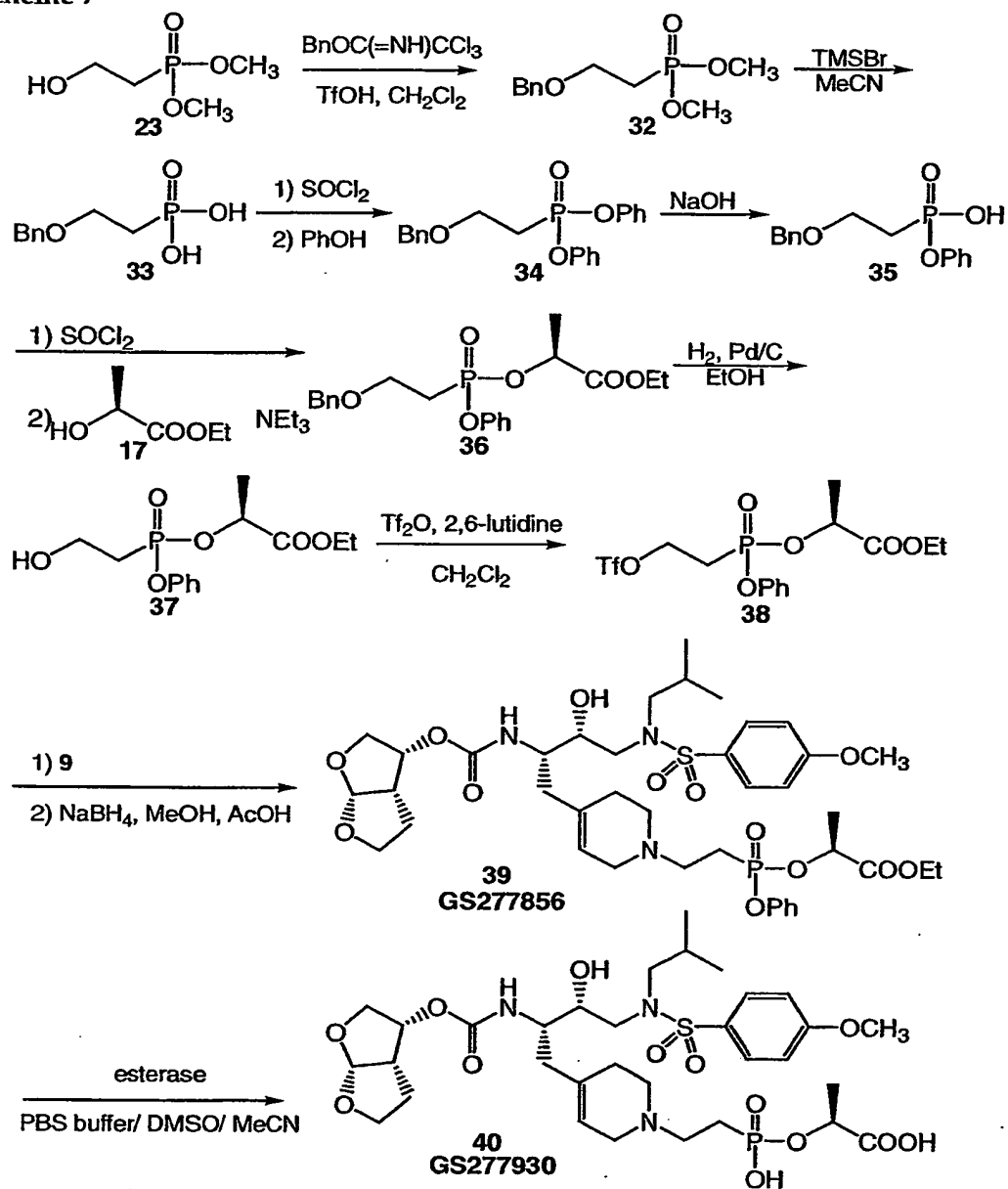
5 ## Example 23

Benzylether 32: A solution of dimethyl hydroxyethylphosphonate (5.0 g, 32.5 mmol, Across)
and benzyl 2,2,2-trichloroacetimidate (97.24 mL, 39.0 mmol, Aldrich) in CH$_2$Cl$_2$ (100 mL) at
0°C under a nitrogen atmosphere was treated with trifluoromethanesulfonic acid (0.40 mL).
Stirring was performed for three hours at 0°C and the reaction was then allowed to warm to

room temperature while stirring continued. The reaction continued for 15 hours, and the reaction mixture was then diluted with dichloromethane, washed with saturated sodium bicarbonate, washed with brine, dried (MgSO$_4$), concentrated under reduced pressure and chromatographed on silica gel eluting with a gradient of eluent from 60% EtOAc in hexane to

5   100% EtOAc to afford 4.5 g, (57%) of the benzyl ether as a colorless liquid. ^{31}P NMR (CDCl$_3$) δ 31.5.

Example 24

Diacid 33: A solution of benzylether 32 (4.5 g, 18.4 mmol) was dissolved in anhydrous

10 acetonitrile (100mL), chilled to 0°C under a nitrogen atmosphere and treated with TMS bromide (9.73 mL, 74mmol). The reaction mixture was warmed to room temperature and after 15 hours of stirring was concentrated repeatedly with MeOH/water to afford the diacid, which was used directly in the next step. ^{31}P NMR (CDCl$_3$) δ 31.9.

15 Example 25

Diphenylphosphonate 34 : Diacid 33 (6.0 g, 27 mmol) was dissolved in toluene and concentrated under reduced pressure three times, dissolved in anhydrous acetonitrile, stirred under a nitrogen atmosphere, and treated with thionyl chloride (20 mL, 270 mmol) by slow addition. The solution was heated to 70°C for two hours, then cooled to room temperature,

20 concentrated and dissolved in anhydrous dichloromethane, chilled to -78°C and treated with phenol (15 g, 162 mmol) and triethylamine (37 mL, 270 mmol). The reaction mixture was warmed to room temperature and stirred for 15 hours, and was then diluted with ice cold dichloromethane, washed with ice cold 1 N. NaOH, washed with ice cold water, dried (MgSO$_4$), and concentrated under reduced pressure. The resulting residue was used directly

25 in the next step. ^{1}H NMR (CDCl$_3$) δ 7.40-7.16 (d, 15H), 4.55 (s, 2H), 3.98-3.84 (m, 2H), 2.55-2.41 (m, 2H); ^{31}P NMR (CDCl$_3$) δ 22.1.

Example 26

Mono acid 35: Monoacid 35 was prepared using conditions analogous to those used to

30 prepare monoacid 16, except that diphenylphosphonate 34 was substituted for benzylether 15. ^{1}H NMR (CDCl$_3$) δ 7.38-7.16 (d, 10H), 4.55 (s, 2H), 3.82-3.60 (m, 3H), 2.33-2.21 (m, 2H); ^{31}P NMR (CDCl$_3$) δ 29.0.

<u>Example 27</u>

Ethyl lactate phosphonate 36: Ethyl lactate phosphonate 36 was prepared analogously to
ethyl lactate phosphonate 18 except monoacid 35 was substituted for monoacid 16. ^{31}P NMR

5   (CDCl$_3$) δ 27.0, 25.6.

<u>Example 28</u>

Ethyl lactate phosphonate with free alcohol 37: Ethyl lactate phosphonate with free alcohol
37 was prepared analogously to ethyl lactate phosphonate with free alcohol 19 except that

10   ethyl lactate phosphonate 36 was substituted for ethyl lactate phosphonate 18. ^{31}P NMR
(CDCl$_3$) δ 28.9, 26.8.

<u>Example 29</u>

Triflate 38: A solution of the alcohol 37 (663 mg, 2.19 mmol) and 2,6-lutidine (0.385 mL,

15   3.31 mmol, Aldrich) in CH$_2$Cl$_2$ (5 mL) was stirred at −45°C as trifluoromethanesulfonic
anhydride (0.48 mL, 2.85 mmol, Aldrich) was added. The solution was stirred for 1.5 h at
−45°C, diluted with ice-cold water (50 mL), and extracted with EtOAc (30 mL x 2). The
combined extracts were washed with ice cold water (50 mL), dried (MgSO$_4$), and
concentrated under reduced pressure to obtain a crude mixture of two diastereomers (910 mg,

20   96%, 1:3 ratio): ^{1}H NMR (acetone-d$_6$) δ 7.48-7.37 (m, 2H), 7.37-7.18 (m, 3H), 5.2-4.95 (m,
3H), 4.3-4.02 (m, 2H), 3.38-3.0 (m, 1H), 3.0-2.7 (m, 2H), 2.1-1.9 (m, 1H), 1.52 (d, 1H), 1.4
(d, 2H), 1.4-1.1)m, 3H); ^{31}P NMR (acetone-d$_6$) δ 21.8 (0.75P), 20.5 (0.25P).

<u>Example 30</u>

25   The prodrug 39: A solution of the crude triflate 38 (499 mg, 1.15 mmol) and the pyridine 9
(494 mg, 0.877 mmol) in acetone (5 mL) was stirred at room temperature for 16.5 h. The
solution was concentrated under reduced pressure to obtain the crude pyridinium salt.
To a solution of the crude pyridinium salt in ethanol (10 mL) was added 5 drops of a solution
of acetic acid (1 mL) in ethanol (5 mL). The solution was stirred at 0°C as NaBH$_4$ (~10 mg,

30   Aldrich) was added. The solution was maintained to be pH 3-4 by adding the acetic acid
solution. More NaBH$_4$ and the acetic acid were added until the reduction was completed.
After 5.5 h, the mixture was concentrated under reduced pressure and the remaining residue
was dissolved in ice-cold saturated NaHCO$_3$ (50 mL). The product was extracted with ice-

cold EtOAc (30 mL x 2) and the combined extracts were washed with 50% saturated
NaHCO$_3$ (50 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue
was purified by a chromatography on silica gel followed by a chromatography on C18
reverse phase column material. Lyophilization of the collected fraction resulted the product

5   39 mixture (376 mg, 50%, ~2.5:1 ratio) as trifluoroacetic acid salt: ^{1}H NMR (CD$_3$CN+TFA)
δ 7.78 (d, 2H, J = 8.7 Hz), 7.52-7.42 (m, 2H); 7.37-7.22 (m 3H), 7.10 (d, 2H, J = 8.7 Hz),
5.78 (d, 1H, J = 9.0 Hz), 5.64 (m, 1H), 5.50 (br, 1H), 5.08 (m, 2H), 4.31-4.12 (m, 2H), 4.04-
3.42 (m, 11H), 3.90 (s, 3H), 3.29 (m, 2H), 3.23 -3.16 (m, 1H), 3.08-2.78 (m, 6H), 2.76-2.27
(m, 5H), 2.23-2.11 (m, 1H), 2.08-1.77 (m, 3H),1.58 (d, 0.9H, J = 7.2 Hz),1.45 (d, 2.1H, J =

10 6.6 Hz), 1.32-1.20 (m, 3H), 0.95 - 0.84 (m, 6H); ^{31}P NMR (CD$_3$CN+TFA) δ 24.1 and 23.8,
22.2 and 22.1; MS (ESI) 852 (M+H).

Example 31

Metabolite 40: To a solution of the prodrug 39 (35.4 mg, 0.037 mmol) in DMSO (0.35 mL)

15 and acetonitrile (0.70 mL) was added 0.1 M PBS buffer (10.5 mL) mixed thoroughly to result
a suspension. To the suspension was added porcine liver esterase suspension (0.175 mL,
EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 6.5 h, the mixture was
filtered through 0.45 um membrane filter and the filtrate was purified by HPLC. The
collected fraction was lyophilized to result the product 40 as trifluoroacetic acid salt (28.8

20 mg, 90%): ^{1}H NMR (D$_2$O) δ 7.96 (d, 2H, J = 8.7 Hz), 7.32 (d, 2H, J = 8.7 Hz), 5.89 (d, 1H, J
= 5.1 Hz), 5.66 (br, 1H), 5.27 (m, 1H), 4.97 (m, 1H), 4.23-4.12 (m, 2H), 4.08 (s, 3H), 4.06-
3.10 (m, 14H), 3.03 (dd, 1H, J = 14.1 and 6.6 Hz), 2.78-1.97 (m, 9H), 1.66 (d, 3H, J = 6.9
Hz),1.03 (d, 3H, J = 7.5 Hz),1.01 (d, 3H, J = 6.9 Hz); ^{31}P NMR (CD$_3$CN+TFA) δ 20.0, 19.8;
MS (ESI) 748 (M+H).

Scheme 8

46: R = Bn
47: R = H

pyBOP, DIEA
——————→
DMF
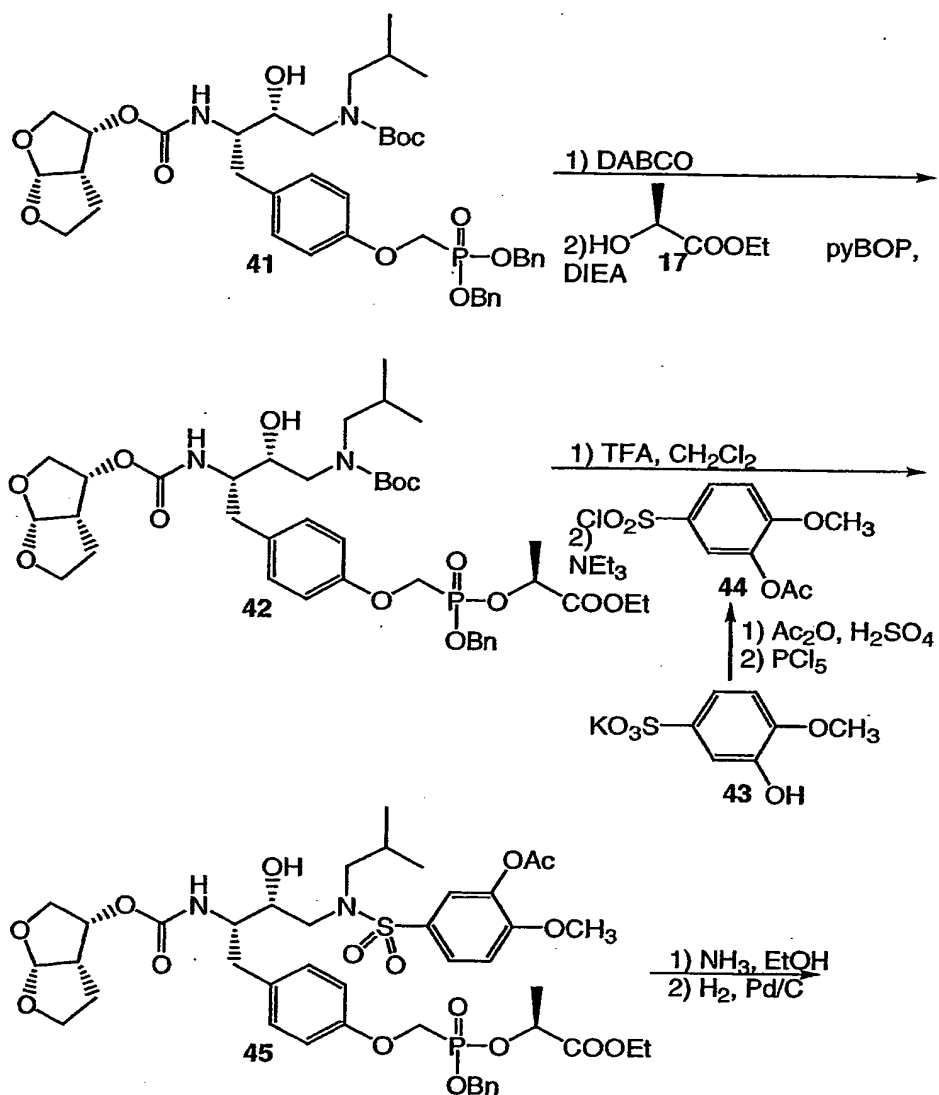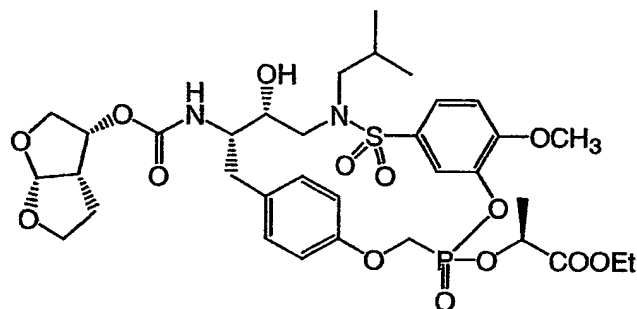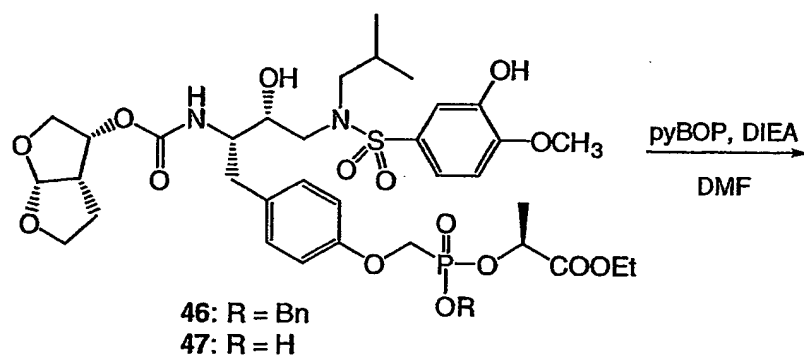
48A: a minor diastereomer (**GS277932**)
48B: a major diastereomer (**GS277933**)

<u>Example 32</u>

Compound 42: The dibenzyl phosphonate **41** (947 mg, 1.21 mmol) was treated with DABCO

5   (140.9 mg, 1.26mmol, Aldrich) in 4.5 mL toluene to obtain the monoacid (890 mg, 106%).
The crude monoacid (890 mg) was dried by evaporation with toluene twice and dissolved in
DMF (5.3 mL) with ethyl (*S*)-lactate (0.3 mL, 2.65 mmol, Aldrich) and pyBOP (945 mg, 1.82
mmol, Aldrich) at room temperature. After diisopropylethylamine (0.85 mL, 4.88 mmol,
Aldrich) was added, the solution was stirred at room temperature for 4 h and concentrated

10 under reduced pressure to a half volume. The resulting solution was diluted with 5% aqueous
HCl (30 mL) and the product was extracted with EtOAc (30 mL x 3). After the combined
extracts were dried (MgSO₄) and concentrated, the residue was chromatographed on silica gel
to afford the compound **42** (686 mg, 72%) as a mixture of two diastereomers (2:3 ratio): ^{1}H
NMR (CDCl₃) δ 7.46-7.32 (m, 5H), 7.13 (d, 2H, J = 8.1 Hz), 6.85 (t, 2H, J = 8.1 Hz), 5.65

15 (m, 1H), 5.35-4.98 (m, 4H), 4.39 (d, 0.8H, J = 10.2 H), 4.30-4.14 (m, 3.2H), 3.98 (dd, 1H, J =
9.3 and 6.0 Hz), 3.92-3.78 (m, 3H), 3.78-3.55 (m, 3H), 3.16-2.68 (m, 6H), 1.85 (m, 1H),
1.74-1.55 (m, 2H), 1.56 (d, 1.8H, J = 7.2 Hz), 1.49 (d, 1.2H), 1.48 (s, 9H), 1.30-1.23 (m, 3H),
0.88 (d, 3H, J = 6.3 Hz), 0.87 (d, 3H, J = 6.3 Hz); ^{31}P NMR (CDCl₃) δ 20.8 (0.4P), 19.5
(0.6P); MS (ESI) 793 (M+H).

Example 33

Compound 45: A solution of compound 42 (101 mg, 0.127 mmol) and trifluoroacetic acid
(0.27 mL, 3.5 mmol, Aldrich) in CH₂Cl₂ (0.6 mL) was stirred at 0°C for 3.5 h and

5   concentrated under reduced pressure. The resulting residue was dried in vacuum to result the
crude amine as TFA salt.

A solution of the crude amine salt and triethylamine (0.072 mL, 0.52 mmol, Aldrich) in
CH₂Cl₂ (1 mL) was stirred at 0°C as the sulfonyl chloride 42 (37 mg, 0.14 mmol) was added.
After the solution was stirred at 0°C for 4 h and 0.5 h at room temperature, the reaction

10   mixture was diluted with saturated NaHCO₃ (20 mL) and extracted with EtOAc (20 mL x 1;
15 mL x 2). The combined organic fractions were washed with saturated NaCl solution,
dried (MgSO₄), and concentrated under reduced pressure. Purification by chromatography on
silica gel provided the sulfonamide 45 (85 mg, 72%) as a mixture of two diastereomers (~1:2
ratio): ^{1}H NMR (CDCl₃) δ 7.45-7.31 (m, 7H), 7.19 (d, 1H, J = 8.4 Hz), 7.12 (d, 2H, J = 7.8

15   Hz), 6.85 (m, 2H), 5.65 (d, 1H, J = 5.4 Hz), 5.34-5.16 (m, 2H), 5.13-4.97 (m, 2H), 4.97-4.86
(m, 1H), 4.38 (d, 0.7H, J = 10.8 Hz), 4.29-4.12 (m, 3.3H), 3.96 (dd, 1H, J = 9.3 and 6.3 Hz),
3.89 (s, 3H), 3.92-3.76 (m, 3H), 3.76-3.64 (m, 2H), 3.64-3.56 (br, 1H), 3.34-3.13 (m, 1H),
3.11-2.70 (m, 6H), 2.34 (s, 3H), 1.86 (m, 1H, J = 7.0 Hz), 1.75-1.58 (m, 2H), 1.56 (d, 2H, J
= 7.2 Hz), 1.49 (d, 1H, J = 7.2 Hz), 1.29-1.22 (m, 3H), 0.94 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H,

20   J = 6.9 Hz); ^{31}P NMR (CDCl₃) δ 20.7 (0.3P), 19.5 (0.7P); MS (ESI) 921 (M+H).

Example 34

Compound 46: Compound 45 (257 mg, 0.279 mmol) was stirred in a saturated solution of
ammonia in ethanol (5 mL) at 0°C for 15 min and the solution was concentrated under

25   reduced pressure. Purification of the residue by chromatography on silica gel provided
compound 46 (2.6 mg, 84%): ^{1}H NMR (CDCl₃) δ 7.48-7.34 (m, 4H), 7.22-7.05 (m, 5H),
7.01 (d, 1H, J = 8.1 Hz), 6.87-6.80 (m, 2H), 5.68 (d, 1H, J = 4.8 Hz), 5.32 (dd, 1.3H, J = 8.7
and 1.8 Hz), 5.22 (d, 0.7H, J = 9.0 Hz), 5.11-5.00 (m, 3H), 4.47-4.14 (m, 4H), 4.00 (dd, 1H, J
= 9.9 and 6.6 Hz), 3.93 (s, 3H), 3.95-3.63 (m, 5H), 3.07-2.90 (m, 4H), 2.85-2.75 (m, 1H),

30   2.75-2.63 (m, 2H), 1.88-1.67 (m, 3H), 1.65-1.55 (m, 2H), 1.57 (d, 2H, J = 6.9 Hz), 1.50 (d,
1H, J = 7.2 Hz), 1.31-1.20 (m, 3H), 0.95 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.3 Hz); ^{31}P
NMR (CDCl₃) δ 20.7 (0.3P), 19.6 (0.7P); MS (ESI) 879 (M+H).

Example 35

Compound 47: A mixture of compound 46 (176 mg, 0.200 mmol) and 10% Pd/C (9.8 mg, Aldrich) in EtOAc (4 mL) and ethanol (1 mL) was stirred under H_2 atmosphere for 3 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated

5   to dryness to afford compound 47 (158 mg, 100%) as white powder: ^{1}H NMR (CDCl$_3$) δ 7.30-7.16 (m, 2H), 7.12 (d, 2H, J = 7.5 Hz), 7.01 (d, 1H, J = 7.8 Hz), 6.84 (d, 2H, J = 7.5 Hz), 5.66 (d, 1H, J = 4.5 Hz), 5.13-4.97 (m, 2H), 4.38-4.10 (m, 4H), 3.93 (s, 3H), 4.02-3.66 (m, 6H), 3.13-2.69 (m, 7H), 1.96-1.50 (m, 3H), 1.57 (d, 3H, J = 6.6 Hz), 1.26 (t, 3H, J = 7.2 Hz), 0.93 (d, 3H, J = 6.0 Hz), 0.88 (d, 3H, J = 6.0 Hz); ^{31}P NMR (CDCl$_3$) δ 20.1; MS (ESI)

10   789 (M+H).

Example 36

Compound 48A and 48B: A solution of pyBOP (191 mg, 0.368 mmol, Aldrich) and diisopropylethylamine (0.1 mL, 0.574 mmol, Aldrich) in DMF (35 mL) was stirred at room

15   temperature as a solution of compound 47 (29 mg, 0.036 mmol) in DMF (5.5 mL) was added over 16 h. After addition, the solution was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was dissolved in ice-cold water and extracted with EtOAc (20 mL x 1; 10 mL x 2). The combined extracts were dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by chromatography on

20   silica gel followed by preparative TLC gave two isomers of structure 48 (1.0 mg, 3.6% and 3.6 mg, 13%). Isomer 48A: ^{1}H NMR (CDCl$_3$) δ 7.39 (m, 1H), 7.12 (br, 1H), 7.01 (d, 2H, J = 8.1 Hz), 6.98 (br, 1H), 6.60 (d, 2H, J = 8.1 Hz), 5.75 (d, 1H, J = 5.1 Hz), 5.37-5.28 (m, 2H), 5.18 (q, 1H, J = 8.7 Hz), 4.71 (dd, 1H, J = 14.1 and 7.5 Hz), 4.29 (m, 3H), 4.15-4.06 (m, 1H), 3.99 (s, 3H), 4.05-3.6 (m, 5H), 3.35 (m, 1H), 3.09 (br, 1H), 2.90-2.78 (m, 3H), 2.2-2.0 (m,

25   3H), 1.71 (d, 3H, J = 6.6 Hz), 1.34 (t, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.3 Hz), 0.95 (d, 3H, J = 6.3 Hz); ^{31}P NMR (CDCl$_3$) δ 17.8; MS (ESI) 793 (M+Na); isomer 48B: ^{1}H NMR (CDCl$_3$) δ 7.46 (d, 1H, J = 9.3 Hz), 7.24 (br, 1H), 7.00 (d, 2H, J = 8.7 Hz), 6.91 (d, 1H, J = 8.7 Hz), 6.53 (d, 2H, J = 8.7 Hz), 5.74 (d, 1H, J = 5.1 Hz), 5.44 (m, 1H), 5.35 (d, 1H, J = 9.0 Hz), 5.18 (q, 1H, J = 7.2 Hz), 4.68 (dd, 1H, J = 14.4 and 6.3 Hz), 4.23 (m, 3H), 4.10 (m, 1H), 4.04 (s,

30   3H), 3.77-4.04 (m, 6H), 3.46 (dd, 1H, J = 12.9 and 11.4 Hz), 3.08 (br, 1H), 2.85 (m, 2H), 2.76 (dd, 1H, J = 12.9 and 4.8 Hz), 1.79-2.11 (m, 3H), 1.75 (d, 3H, J = 6.6 Hz), 1.70 (m, 2H),

1.27 (t, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz); ^{31}P NMR (CDCl$_3$)
δ 15.4; MS (ESI) 793 (M+Na).

Example 1

1
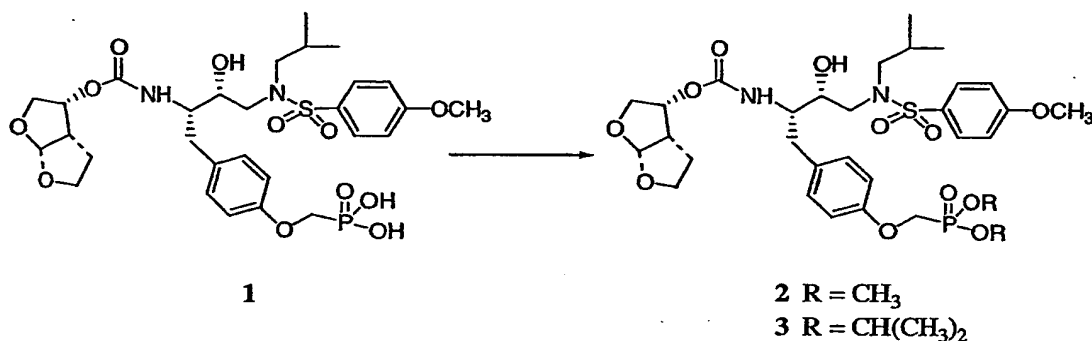
2 R = CH$_3$
3 R = CH(CH$_3$)$_2$

Example 1A

Dimethylphosphonic ester **2** (R = CH$_3$): To a flask was charged with phosphonic acid **1** (67
mg, 0.1 mmol), methanol (0.1 mL, 2.5 mmol) and 1, 3-dicyclohexylcarbodiimide (83 mg, 0.4
mmol), then pyridine (1 mL) was added under N$_2$. The resulted mixture was stirred at 60
–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture
was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and
the combined organic phase was washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$,
filtered and concentrated. The residue was purified by chromatography on silica gel
(isopropanol/CH$_2$Cl$_2$, 1% to 7%) to give **2** (39 mg, 56 %) as a white solid. ^{1}H NMR (CDCl$_3$)
δ 7.71(d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7
Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.10-4.92 (m, 4H), 4.26 (d, J = 9.9 Hz, 2H), 3.96 -3.65 (m
overlapping s, 15H), 3.14-2.76 (m, 7H), 1.81-1.55 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.88 (d,
J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 21.7; MS (ESI) 723 (M+Na).

Example 1B

Diisopropylphosphonic ester **3** (R = CH (CH$_3$)$_2$) was synthesized in the same manner in 60%
yield. ^{1}H NMR (CDCl$_3$) δ 7.71(d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7Hz, 2H), 7.15 (d, J = 8.7
Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.08-4.92
(m, 3H), 4.16 (d, J = 10.5 Hz, 2H), 3.98 -3.68 (m overlapping s, 9H), 3.16-2.78 (m, 7H),

1.82-1.56 (m, 3H), 1.37 (t, J = 6.3 Hz, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.3; MS (ESI) 779 (M+Na).

Example 2

4   5
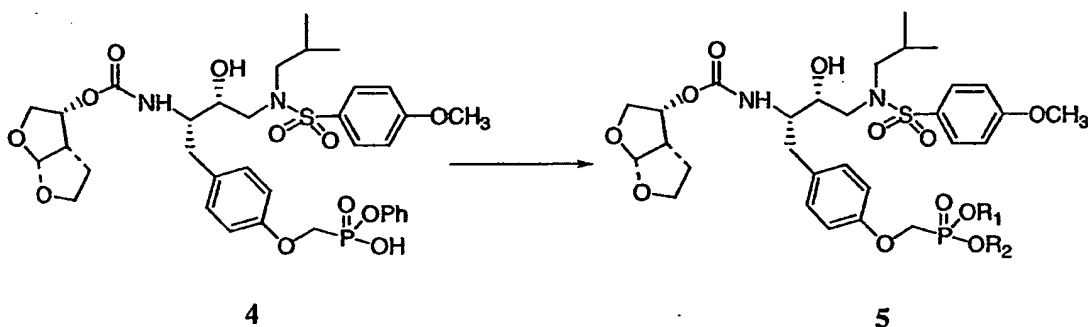
Compound	R$_1$	R$_2$
5a	OPh	mix-Hba-Et
5b	OPh	(S)-Hba-Et
5c	OPh	(S)-Hba-tBu
5d	OPh	(S)-Hba-EtMor
5e	OPh	(R)-Hba-Et

Example 2A

Monolactate 5a (R1 = OPh, R2 = Hba-Et): To a flask was charged with monophenyl phosphonate 4 (250 mg, 0.33 mmol), 2-hydroxy-n-butyric acid ethyl ester (145 mg, 1.1 mmol) and 1, 3-dicyclohexylcarbodiimide (226 mg, 1.1 mmol), then pyridine (2.5 mL) was added under N$_2$. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH$_2$Cl$_2$, 1:1) to give 5a (150 mg, 52 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.70 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.21 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.5 and 15.1; MS (ESI) 885 (M+Na).

Example 2B

Monolactate 5b (R1 = OPh, R2 = (S)-Hba-Et): To a flask was charged with monophenyl phosphonate 4 (600 mg, 0.8 mmol), (S)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was

5   added under N$_2$. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH$_2$Cl$_2$, 1:1) to give 5b (360

10   mg, 52 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.5 and 15.2; MS (ESI) 885 (M+Na).

15

Example 2C

Monolactate 5c(R1 = OPh, R2 = (S)-Hba-tBu): To a flask was charged with monophenyl phosphonate 4 (120 mg, 0.16 mmol), tert-butyl (S)-2-hydroxybutyrate (77 mg, 0.48 mmol) and 1, 3-dicyclohexylcarbodiimide (99 mg, 0.48 mmol), then pyridine (1 mL) was added

20   under N$_2$. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH$_2$Cl$_2$, 1:1) to give 5c (68 mg,

25   48 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.64 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.44 (d, J = 11 Hz, 9H), 1.04-0.86 (m, 9H); ^{31}P NMR (CDCl$_3$) δ 17.5 and15.2; MS (ESI) 913 (M+Na).

30

Example 2D

Monolactate 5d (R1 = OPh, R2 = (S)-Lac-EtMor): To a flask was charged with monophenyl phosphonate 4 (188 mg, 0.25 mmol), (S)-lactate ethylmorpholine ester (152 mg, 0.75 mmol)

and 1, 3-dicyclohexylcarbodiimide (155 mg, 0.75 mmol), then pyridine (2mL) was added under N$_2$. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was

5   washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH$_2$Cl$_2$, 1:9) to give 5d (98 mg, 42 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.34-7.20 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.57-4.20 (m, 4H), 3.97 -3.63 (m overlapping

10   s, 13H), 3.01-2.44 (m, 13H), 1.85-1.50 (m, 6H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4 and 15.3; MS (ESI) 934(M).

Example 2E

Monolactate 5e (R1 = OPh, R2 = (R)-Hba-Et): To a flask was charged with monophenyl

15   phosphonate 4 (600 mg, 0.8 mmol), (R)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under N$_2$. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was

20   washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH$_2$Cl$_2$, 1:1) to give 5e (345 mg, 50 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.70 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m

25   overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.5 and 15.1; MS (ESI) 885 (M+Na).

4   **6**
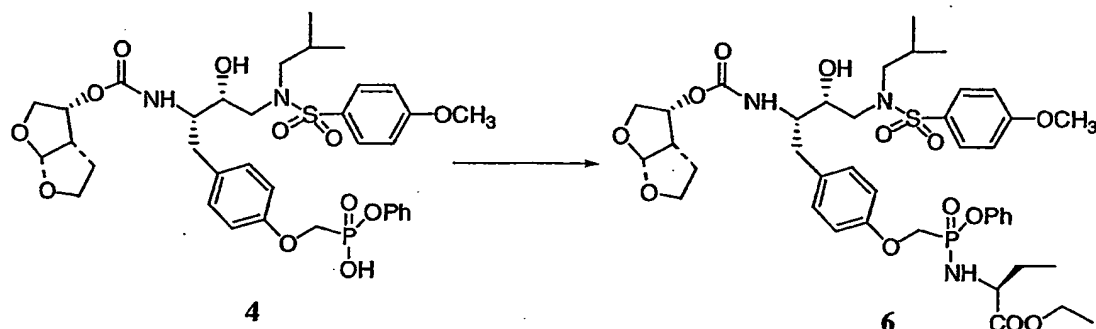
Example 3

Monoamidate **6**: To a flask was charged with monophenyl phosphonate **4** (120 mg, 0.16 mmol), L-alanine butyric acid ethyl ester hydrochloride (160 mg, 0.94 mmol) and 1, 3-dicyclohexylcarbodiimide (132 mg, 0.64 mmol), then pyridine (1 mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH_2Cl_2, 1:9) to give **6** (55 mg, 40 %) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.37-7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1Hz, 1H), 5.10-4.92 (m, 3H), 4.28 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.7 and 19.6; MS (ESI) 884(M+Na).

7

8

9
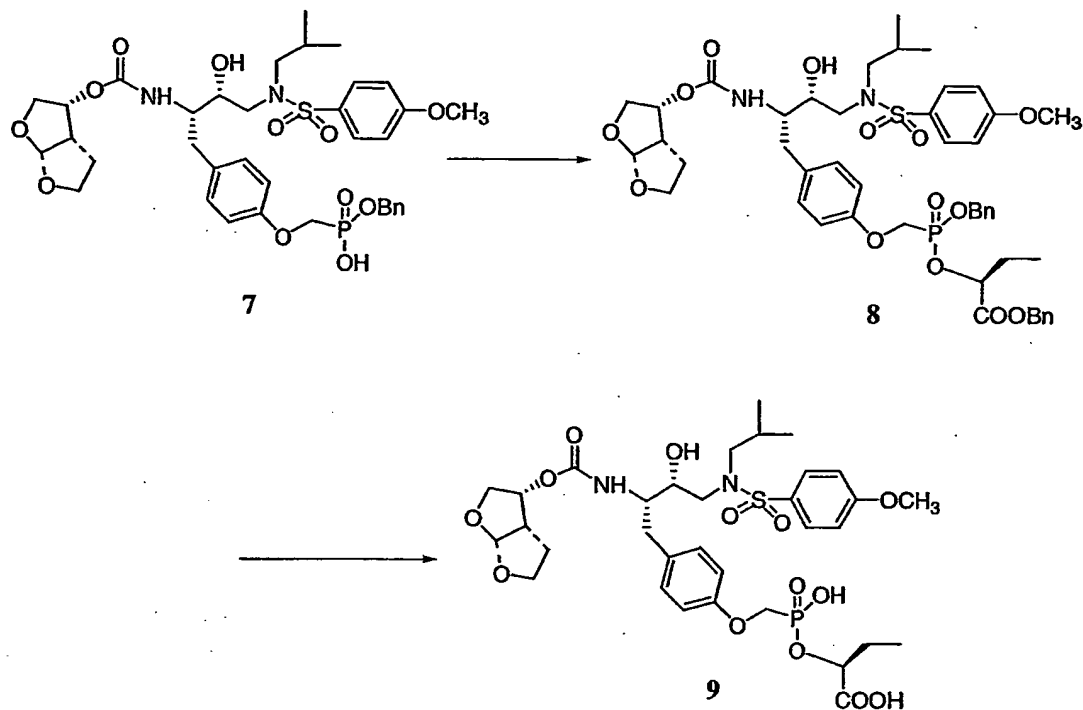
Example 4A

Compound **8**: To a stirred solution of monobenzyl phosphonate **7** (195 mg, 0.26mmol) in 1
mL of DMF at room temperature under N_2 was added benzyl-(s)-lactate (76 mg, 0.39 mmol)

5   and PyBOP (203 mg, 0.39mmol), followed by DIEA (181μL, 1 mmol). After 3 h, the solvent
was removed under reduced pressure, and the resulting crude mixture was purified by
chromatography on silica gel (ethyl acetate/hexane 1:1) to give **8** (120 mg, 50%) as a white
solid. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.12 (d, J = 8.7 Hz,
2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.24-4.92 (m,

10   7H), 4.28 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.16-2.76 (m, 7H), 1.95-1.62 (m, 5H),
0.99-0.87 (m, 9H); ^{31}P NMR (CDCl$_3$) δ 21.0 and 19.7; MS (ESI) 962 (M+Na).

Example 4B

Compound **9**: A solution of compound **8** (100 mg) was dissolved in EtOH/ EtOAc (9 mL/

15   3mL), treated with 10 % Pd/C (10 mg) and was stirred under H_2 atmosphere (balloon) for 1.5
h. The catalyst was removed by filtration through celite. The filtered was evaporated under
reduced pressure, the residue was triturated with ether and the solid was collected by
filtration to afford the compound **9** (76mg, 94%) as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.76
(d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz,

20   2H), 5.59 (d, J = 5.4 Hz, 1H), 5.03-4.95 (m, 2H), 4.28 (m, 2H), 3.90 -3.65 (m overlapping s,

9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 1.96 (m, 3H), 1.61 (m, 2H), 1.18 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 18.3; MS (ESI) 782 (M+Na).

10 → **11**

→ **12**
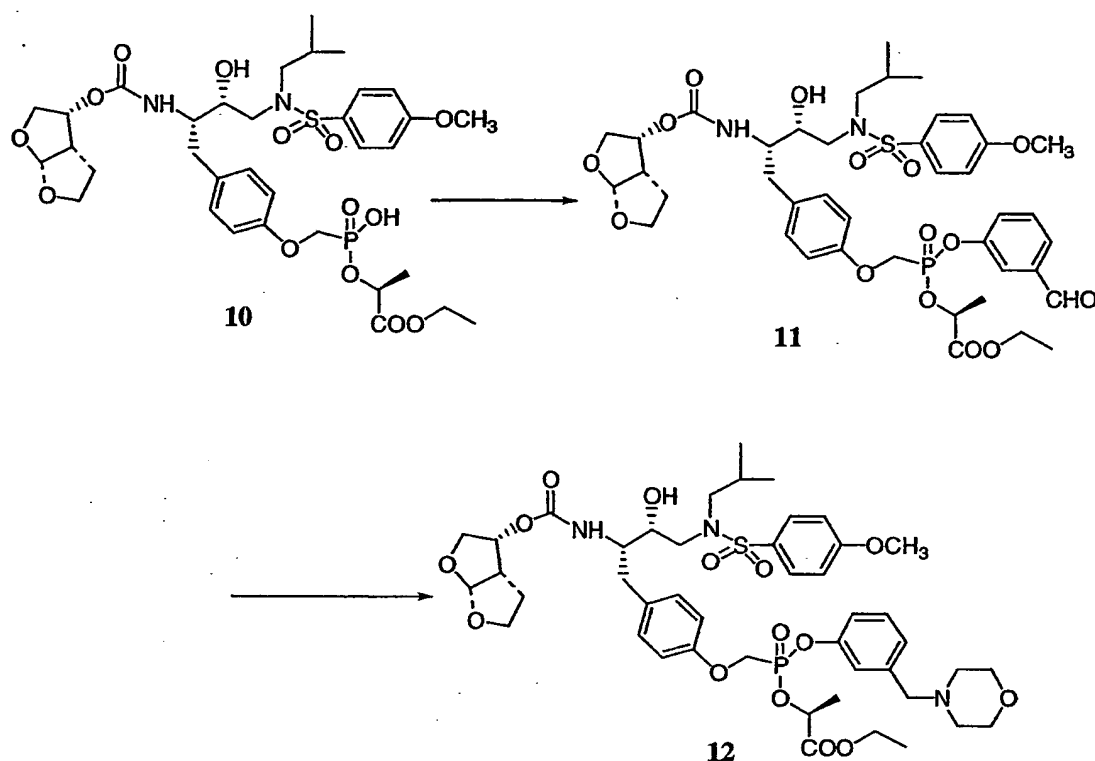
Example 5A

Compound **11**: To a stirred solution of compound **10** (1 g, 1.3mmol) in 6 mL of DMF at room temperature under N$_2$ was added 3-hydroxybenzaldehyde (292 mg, 2.6 mmol) and PyBOP (1 g, 1.95mmol), followed by DIEA (0.9 mL, 5.2 mmol). After 5 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give **11** (800 mg, 70%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 9.98 (s, 1H), 7.79-6.88 (m, 12H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.62-4.16 (m, 4H), 3.99 -3.61 (m overlapping s, 9H), 3.11-2.79 (m, 5H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.9 and 15.9; MS (ESI) 899 (M+ Na).

Example 5B

Compound **12**: To a stirred solution of compound **11** (920 mg, 1.05 mmol) in 10 mL of ethyl acetate at room temperature under N$_2$ was added morpholine (460 mg, 5.25 mmol) and acedic

acid (0.25 mL, 4.2 mmol), followed by sodium cyanoborohydride (132 mg, 2.1 mmol). After

20h, the solvent was removed under reduced pressure, and the residue was diluted with ethyl

acetate and the combined organic phase was washed with NH₄Cl, brine and water, dried over

Na₂SO₄, filtered and concentrated. The residue was purified by chromatography on silica gel

5   (isopropanol / CH₂Cl₂, 6%) to give **12** (600 mg, 60%) as a white solid. ^{1}H NMR (CDCl₃) δ

7.71 (d, J = 8.7 Hz, 2H), 7.27 (m, 4H), 7.15 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.89

(m, 2H), 5.65 (m, 1H), 5.21-5.02 (m, 3H), 4.58-4.38 (m, 2H), 4.21-4.16 (m, 2H), 3.99 -3.63

(m overlapping s, 15H), 3.47 (s, 2H), 3.18-2.77 (m, 7H), 2.41 (s, 4H), 1.85-1.53 (m, 6H),

1.25 (m, 3H), 0.90 (m, 6H); ^{31}P NMR (CDCl₃) δ 17.4 and 15.2; MS (ESI) 971 (M+Na).

10
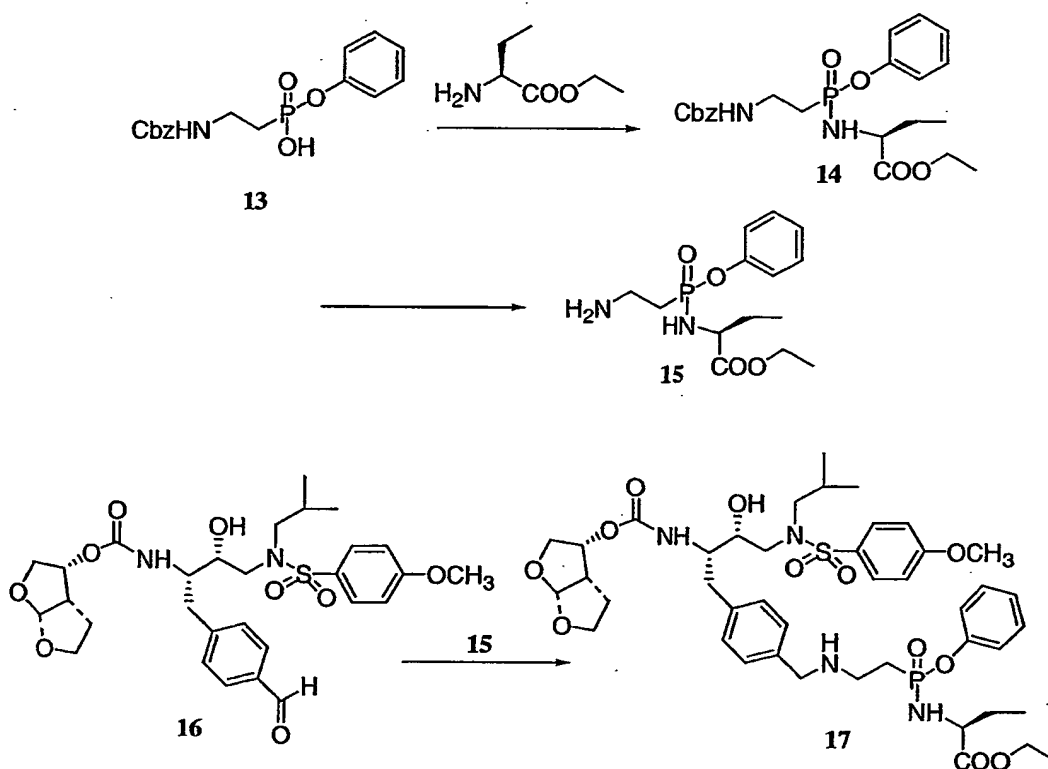
Example 6A

Compound **14**: To a stirred solution of compound **13** (1 g, 3 mmol) in 30 mL of acetonitrile

15   at room temperature under N₂ was added thionyl chloride (0.67 mL, 9 mmol). The resulted

mixture was stirred at 60-70°C for 0.5 h. After cooled to room temperature, the solvent was

removed under reduced pressure, and the residue was added 30 mL of DCM, followed by

DIEA (1.7 mL, 10 mmol), L-alanine butyric acid ethyl ester hydrochloride (1.7 g, 10 mmol)

and TEA (1.7 mL, 12 mmol). After 4h at room temperature, the solvent was removed under

reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography on silica gel (Hexane/EtOAc 1:1) to give **14** (670 mg, 50%) as a yellow oil. ¹H NMR (CDCl₃) δ 7.33-7.11 (m, 10H), 5.70 (m, 1H), 5.10 (s, 2H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.76-1.55 (m, 2H), 1.25-1.19 (m, 3H), 0.85-0.71 (m, 3H); ³¹P NMR (CDCl₃) δ 30.2 and 29.9; MS (ESI) 471 (M+Na).

Example 6B

Compound **15**: A solution of compound **14** (450mg) was dissolved in 9 mL of EtOH, then 0.15 mL of acetic acid and 10 % Pd/C (90 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **15** (300mg, 95%) as a colorless oil. ¹H NMR (CDCl₃) δ 7.29-7.12 (m, 5H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.70-1.55 (m, 2H), 1.24-1.19 (m, 3H), 0.84-0.73(m, 3H); ³¹P NMR (CDCl₃) δ 29.1 and 28.5; MS (ESI) 315 (M+1).

Example 6C

Monoamdidate **17**: To a stirred solution of compound **16** (532 mg, 0.9 mmol) in 4 mL of 1,2-dichloroethane was added compound **15** (300 mg, 0.96 mmol) and MgSO₄ (50 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (1.3 mL, 23 mmol) and sodium cyanoborohydride (1.13 g, 18 mmol) were added. The reaction mixture was stirred at room temperature for 1 h under argon. Then aqueous NaHCO₃ (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH / EtOAc, 1/9) to give **17** (600 mg, 60%) as a white solid. ¹H NMR (CDCl₃) δ 7.73 (d, J = 8.7 Hz, 2H), 7.33-7.13 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.11-4.98 (m, 2H), 4.22 -3.68 (m overlapping s, 15H), 3.20-2.75 (m, 9H), 2.21-2.10 (m, 2H), 1.88-1.55(m, 5H), 1.29-1.19 (m, 3H), 0.94-0.70 (m, 9H); ³¹P NMR (CDCl₃) δ 31.8 and 31.0; MS (ESI) 889 (M).

Example 7
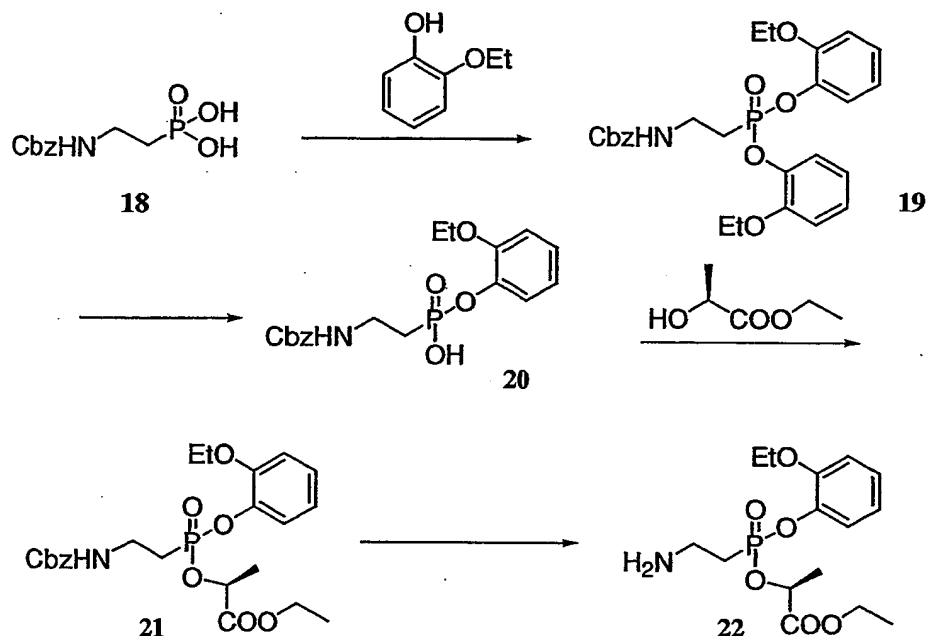
Example 7A

Compound **19**: To a stirred solution of compound **18** (3.7 g, 14.3 mmol) in 70 mL of
acetonitrile at room temperature under N_2 was added thionyl chloride (6.3 mL, 86 mmol).
The resulted mixture was stirred at 60-70°C for 2 h. After cooled to room temperature, the
solvent was removed under reduced pressure, and the residue was added 150 mL of DCM,
followed by TEA (12 mL, 86 mmol) and 2-ethoxyphenol (7.2 mL, 57.2 mmol). After 20h at
room temperature, the solvent was removed under reduced pressure, and the residue was
diluted with ethyl acetate and washed with brine and water, dried over Na_2SO_4, filtered and
concentrated. The residue was purified by chromatography on silica gel (DCM/EtOAc 9:1)
to give **19** (4.2 g, 60%) as a yellow oil. ^1H NMR (CDCl$_3$) δ 7.32-6.83 (m, 13H), 5.22 (m,
1H), 5.12 (s, 2H), 4.12-3.73 (m, 6H), 2.52-2.42 (m, 2H), 1.41-1.37 (m, 6H); ^{31}P NMR
(CDCl$_3$) δ 25.4; MS (ESI) 522 (M+Na).

Example 7B

Compound **20**: A solution of compound **19**(3 g, 6 mmol) was dissolved in 70 mL of
acetonitrile at 0°C, then 2N NaOH (12 mL, 24 mmol) was added dropwisely. The reaction
mixture was stirred at room temperature for 1.5 h. Then the solvent was removed under
reduced pressure, and the residue diluted with water and extracted with ethyl acetate. The
aqueous layer was acidified with conc. HCl to PH = 1, then extracted with ethyl acetate,

combined the organic layer and dried over Na_2SO_4, filtered and concentrated to give compound **20** (2 g, 88%) as a off-white solid. ^1H NMR ($CDCl_3$) δ 7.33-6.79 (m, 9H), 5.10 (s, 2H), 4.12-3.51 (m, 6H), 2.15-2.05 (m, 2H), 1.47-1.33 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 30.5; MS (ESI) 380 (M+1).

5

Example 7C

Compound **21**: To a stirred solution of compound **20** (1 g, 2.6 mmol) in 20 mL of acetonitrile at room temperature under N_2 was added thionyl chloride (1.1 mL, 15.6 mmol). The resulted mixture was stirred at 60-70°C for 45 min. After cooled to room temperature, the solvent was

10   removed under reduced pressure, and the residue was added 25 mL of DCM, followed by TEA (1.5 mL, 10.4 mmol) and (S) lactate ethyl ester (0.9 mL, 7.8 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc 3:1) to give **21**

15   (370 mg, 30%) as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.33- 6.84 (m, 9H), 6.17-6.01 (m, 1H), 5.70 (m, 1H), 5.18-5.01 (m, 3H), 4.25-4.04 (m, 4H), 3.78-3.57 (m, 2H), 2.38-2.27 (m, 2H), 1.5-1.23 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 29.2 and 27.3; MS (ESI) 502 (M+Na).

Example 7D

20   Compound **22**: A solution of compound **21** (370mg) was dissolved in 8 mL of EtOH, then 0.12 mL of acetic acid and 10 % Pd/C (72 mg) was added. The resulted mixture was stirred under H_2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **22** (320mg, 96%) as a colorless oil. ^1H NMR ($CDCl_3$) 7.27- 6.86 (m, 4H), 5.98 (s, 2H), 5.18-5.02 (m, 1H), 4.25-4.06 (m,

25   4H), 3.34-3.24 (m, 2H), 2.44-2.30 (m, 2H), 1.62-1.24 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 28.3 and 26.8; MS (ESI) 346 (M+1).
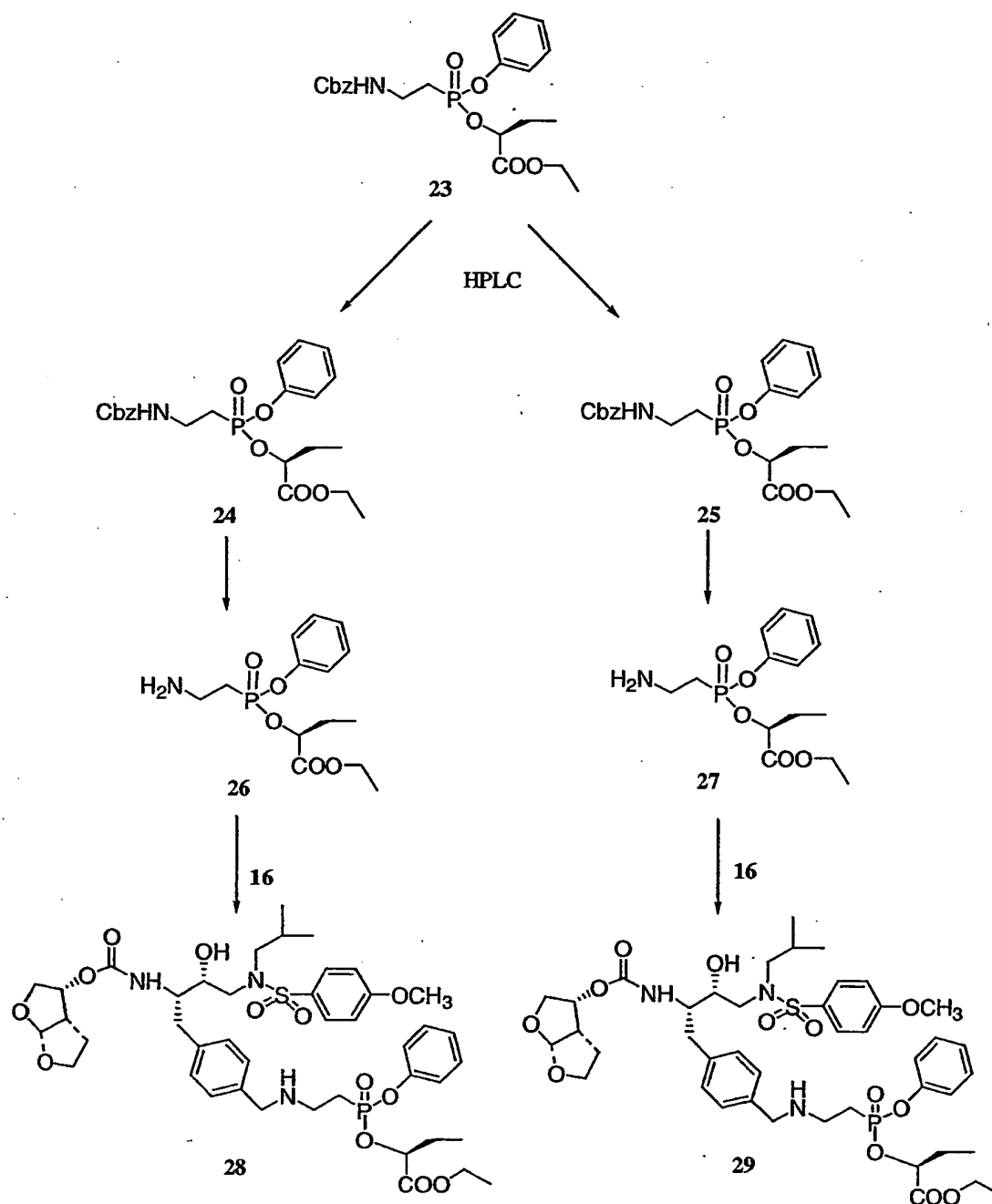
Example 8A

Compound **24**: Compound **23** was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (65:35, v/v) at a flow rate of 70 mL/ min. The injection volume was 4 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.2 min for compound **24** as yellow oil. ^{1}H NMR (CDCl$_3$) δ 7.36-7.19 (m, 10H), 5.88 (m, 1H), 5.12 (s, 2H), 4.90-4.86 (m, 1H),

4.26-4.12 (m, 2H), 3.72-3.61(m, 2H), 2.36-2.29 (m, 2H), 1.79-1.74 (m, 2H); 1.27 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 28.3; MS (ESI) 472 (M+Na).

Example 8B

5   Compound 25 was purified in the same manner and retention time was 7.9 min for compound 25 as yellow oil. ^{1}H NMR (CDCl$_3$) δ 7.34-7.14 (m, 10H), 5.75 (m, 1H), 5.10 (s, 2H), 4.96-4.91 (m, 1H), 4.18-4.12 (m, 2H), 3.66-3.55(m, 2H), 2.29-2.19 (m, 2H), 1.97-1.89 (m, 2H); 1.21 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 26.2; MS (ESI) 472 (M+Na).

10

Example 8C

Compound 26: A solution of compound 24 (1 g) was dissolved in 20 mL of EtOH, then 0.3 mL of acetic acid and 10 % Pd/C (200 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was
15   evaporated under reduced pressure to afford the compound 26 (830mg, 99 %) as a colorless oil. ^{1}H NMR (CDCl$_3$) δ 7.46-7.19 (m, 5H), 4.92-4.81 (m, 1H), 4.24-4.21 (m, 2H), 3.41-3.28 (m, 2H), 2.54-2.38 (m, 2H), 1.79-1.74 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 26.9; MS (ESI) 316 (M+1).

20   Example 8D

Compound 27: A solution of compound 25 (700g) was dissolved in 14 mL of EtOH, then 0.21 mL of acetic acid and 10 % Pd/C (140 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound 27 (510mg, 98 %) as a colorless
25   oil. ^{1}H NMR (CDCl$_3$) δ 7.39-7.18 (m, 5H), 4.98-4.85 (m, 1H), 4.25-4.22 (m, 2H), 3.43-3.28 (m, 2H), 2.59-2.41 (m, 2H), 1.99-1.85 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 24.2; MS (ESI) 316 (M+1).

Example 8E

30   Compound 28: To a stirred solution of compound 16 (1.18 g, 2 mmol) in 9 mL of 1,2-dichloroethane was added compound 26 (830 mg, 2.2 mmol) and MgSO$_4$ (80 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.34

mL, 6 mmol) and sodium cyanoborohydride (251mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous NaHCO$_3$ (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The

5   residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **28** (880 mg, 50 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 6.99 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.03-4.85 (m, 3H), 4.24 -3.67 (m overlapping s, 15H), 3.14-2.70 (m, 9H), 2.39-2.28 (m, 2H), 1.85-1.51 (m, 5H), 1.29-1.25 (m, 3H), 0.93-0.78 (m, 9H); ^{31}P NMR (CDCl$_3$) δ 29.2; MS (ESI) 912 (M+Na).

10

Example 8F

Compound **29**: To a stirred solution of compound **16** (857 g, 1.45 mmol) in 7 mL of 1,2-dichloroethane was added compound **27** (600 mg, 1.6 mmol) and MgSO$_4$ (60 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.23

15   mL, 3 mmol) and sodium cyanoborohydride (183mg, 2.9 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous NaHCO$_3$ (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **29** (650 mg,

20   50 %) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.03-4.90 (m, 3H), 4.17 -3.67 (m overlapping s, 15H), 3.16-2.77 (m, 9H), 2.26-2.19 (m, 2H), 1.94-1.53 (m, 5H), 1.26-1.18 (m, 3H), 1.00-0.87 (m, 9H); ^{31}P NMR (CDCl$_3$) δ 27.4; MS (ESI) 912 (M+Na).
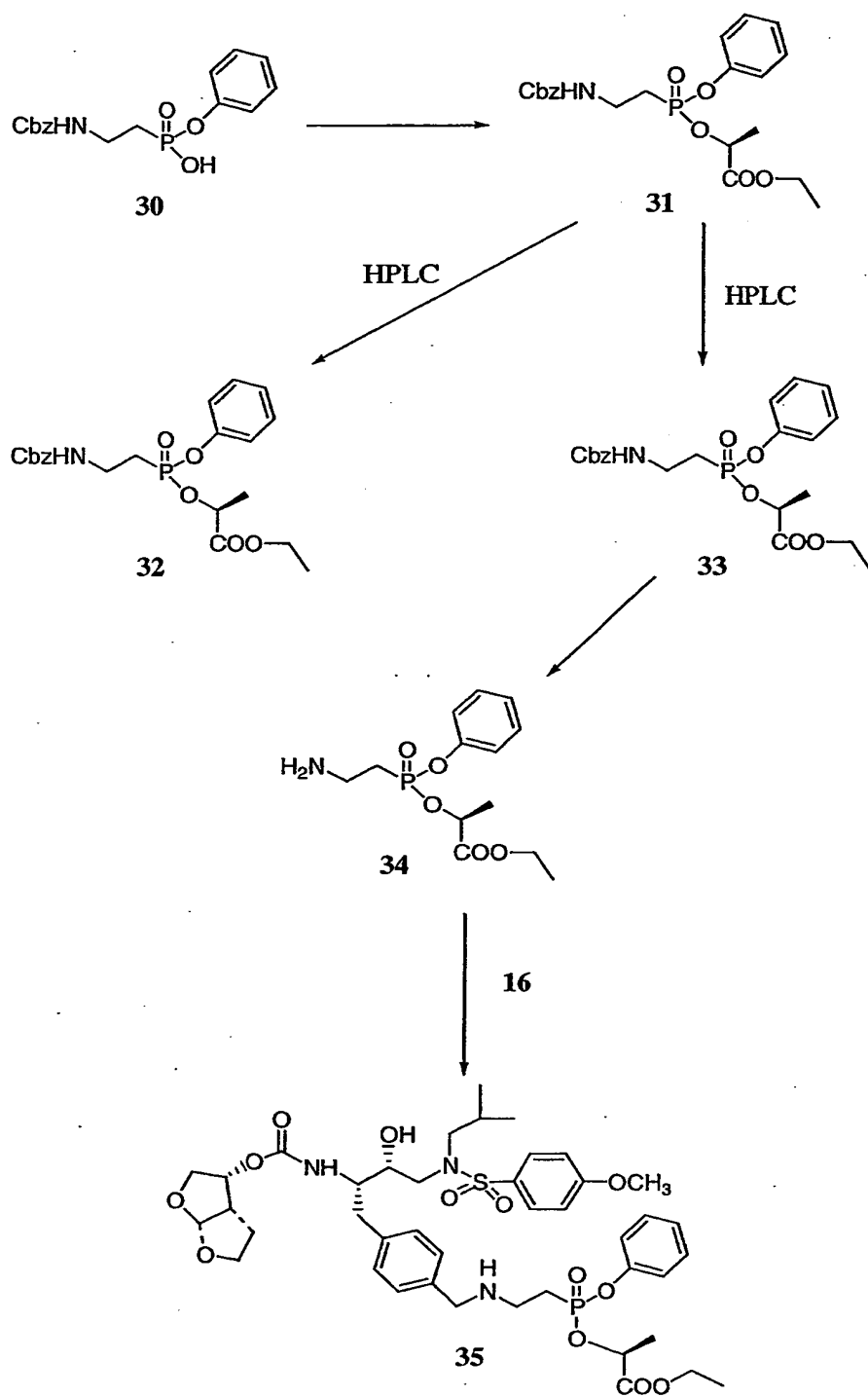
Example 9A

Compound **31**: To a stirred solution of compound **30** (20 g, 60 mmol) in 320 mL of toluene at room temperature under N₂ was added thionyl chloride (17.5 mL, 240 mmol) and a few drops of DMF. The resulted mixture was stirred at 60-70°C for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 280 mL of DCM, followed by TEA (50 mL, 360 mmol) and (S) lactate ethyl ester (17 mL, 150 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc , 1:1) to give **31** (24 g, 92 %) as a yellow oil. ^{1}H NMR (CDCl₃) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); ^{31}P NMR (CDCl₃) δ 28.2 and 26.2; MS (ESI) 458 (M+Na).

Example 9B

Compound **32**: Compound **31** was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (60:40, v/v) at a flow rate of 70 mL/ min. The injection volume was 3 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.1 min for compound **32** as yellow oil. ^{1}H NMR (CDCl₃) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); ^{31}P NMR (CDCl₃) δ 28.2; MS (ESI) 458 (M+Na).

Example 9C

Compound **33** was purified in the same manner and retention time was 7.9 min for compound **33** as yellow oil. ^{1}H NMR (CDCl₃) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); ^{31}P NMR (CDCl₃) δ 26.2; MS (ESI) 458 (M+Na).

Example 9D

Compound **34**: A solution of compound **33** (3.2 g) was dissolved in 60 mL of EtOH, then 0.9 mL of acetic acid and 10 % Pd/C (640 mg) was added. The resulted mixture was stirred

under H$_2$ atmosphere (balloon) for 4 h. After filtration through celite, the filtered was

evaporated under reduced pressure to afford the compound **34** (2.7 g, 99 %) as a colorless oil.

^{1}H NMR (CDCl$_3$) δ 7.42-7.18 (m, 5H), 6.10 (s, 1H), 5.15-5.02 (m, 1H), 4.24-4.05 (m, 2H),

3.25-3.16 (m, 2H), 2.36-2.21 (m, 2H), 1.61-1.58 (m, 3H), 1.35- 1.18, m, 3H); ^{31}P NMR

5   (CDCl$_3$) δ 26.1; MS (ESI) 302 (M+1).

<u>Example 9E</u>

Compound **35**: To a stirred solution of compound **16** (8.9 g, 15 mmol) in 70 mL of 1,2-

dichloroethane was added compound **34** (8.3 g, 23 mmol) and MgSO$_4$ (80 mg), the resulted

10   mixture was stirred at room temperature under argon for 2.5h, then acetic acid (3 mL, 52.5

mmol) and sodium cyanoborohydride (1.9g, 30 mmol) were added. The reaction mixture was

stirred at room temperature for 1.5 h under argon. Then aqueous NaHCO$_3$ (100 mL) was

added, and the mixture was extracted with ethyl acetate, and the combined organic layers

were washed with brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue

15   was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **35** (8.4 g, 64 %) as

a white solid. ^{1}H NMR (CDCl$_3$) δ 7.73 (d, J = 8.7 Hz, 2H), 7.36-7.17(m, 9H), 7.00 (d, J = 8.7

Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.07-4.97 (m, 3H), 4.19 -3.67 (m overlapping s, 13H),

3.15-2.78 (m, 9H), 2.25-2.19 (m, 2H), 1.91-1.54 (m, 6H), 1.24-1.20 (m, 3H), 0.94-0.87 (m,

6H); ^{31}P NMR (CDCl$_3$) δ 27.4; MS (ESI) 876 (M+1).

20

Resolution of Compound 35 Diastereomers

Analysis was performed on an analytical Daicel Chiralcel OD column, conditions described

below, with a total of about 3.5 mg compound **35** free base injected onto the column. This lot

was about a 3:1 mixture of major to minor diastereomers where the lactate ester carbon is a

25   3:1 mix of R and S configurations.

Two injections of 3.8 and 3.5 mg each were made using the conditions described below. The

isolated major diastereomer fractions were evaporated to dryness on a rotary evaporator

under house vacuum. The chromatographic solvents were displaced by two portions of ethyl

acetate followed by a single portion of ethyl acetate – trifluoroacetic acid (about 95:5) and a

30   final high vacuum strip to aid in removal of trace solvents. This yielded the major

diastereomer trifluoroacetate salt as a gummy solid.

The resolved minor diastereomer was isolated for biological evaluation by an 11 mg injection, performed on an analytical Daicel Chiralcel OD column, using the conditions described in below. The minor diastereomer of 35 was isolated as the trifluoroacetate salt by the conditions described above.

5

Larger scale injections (~ 300 mg 35 per injection) were later performed on a Daicel Chiralcel OD column semi-preparative column with a guard column, conditions described below. A minimal quantity of isopropyl alcohol was added to heptane to dissolve the 3:1 diastereomeric mix of 35 and the resolved diastereomers sample, and the isolated fractions

10 were refrigerated until the eluted mobile phase was stripped.

Analytical Column, ~ 4 mg Injection, Heptane – EtOH (20:80) Initial
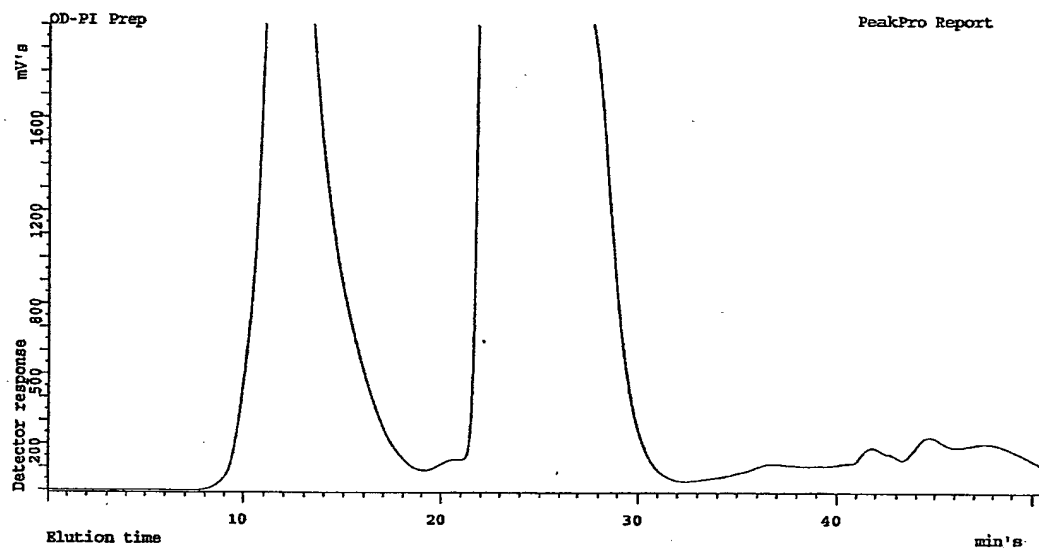
15

HPLC CONDITIONS

Column	: Chiralcel OD, 10 µm, 4.6 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (20:80 initial)
	: 100% Ethyl Alcohol (final)
	Note: Final began after first peak eluted
Flow Rate	: 1.0 mL/min
Run Time	: As needed
Detection	: UV at 250 nm
Temperature	: Ambient
Injection	: ~ 4 mg on Column
Sample Prep.	: Dissolved in ~ 1 mL heptane –
	ethyl alcohol (50:50)
Retention Times	: **35 Minor ~ 14 min**
	: **35 Major ~ 25 min**

Analytical Column, ~ 6 mg Injection, Heptane – EtOH (65:35) Initial
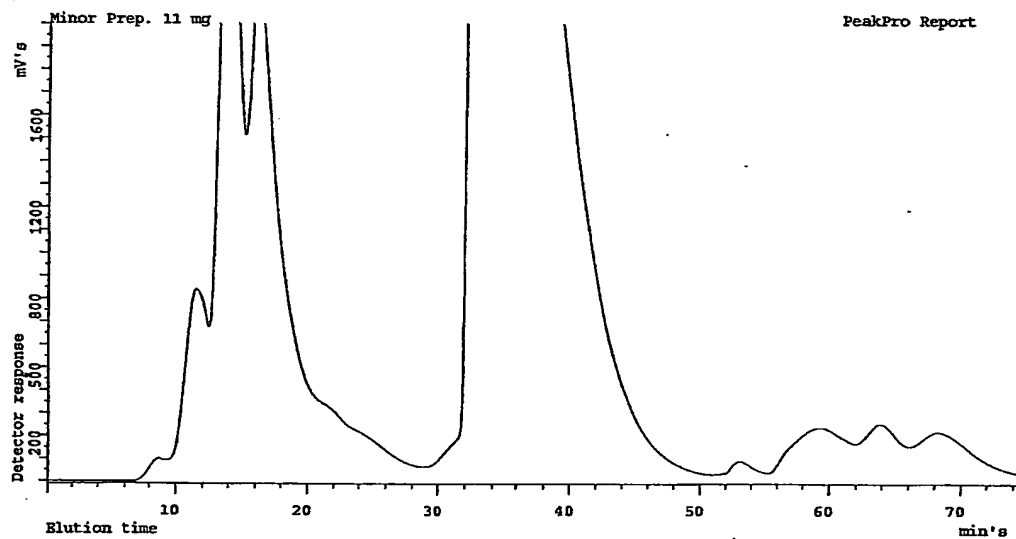
5

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HPLC CONDITIONS

Column   : Chiralcel OD, 10 µm, 4.6 x 250 mm

Mobile Phase   : Heptane – Ethyl Alcohol (65:35 initial)

                    : Heptane – Ethyl Alcohol (57.5:42.5 intermediate)

                      Note: Intermediate began after impurity peaks eluted

                    : Heptane – Ethyl Alcohol (20:80 final)

                      Note: Final mobile phase began after minor

                      diastereomer eluted

Flow Rate   : 1.0 mL/min

Run Time   : As needed

Detection   : UV at 250 nm

Temperature   : Ambient

Injection   : ~ 4 mg on Column

Sample Prep.   : Dissolved in ~ 1 mL heptane –

                      ethyl alcohol (50:50)

Retention Times   : 35 Minor ~ 14 min

                    : 35 Major ~ 40 min

Semi-Preparative Column, ~ 300 mg Injection, Heptane – EtOH (65:35) Initial

5
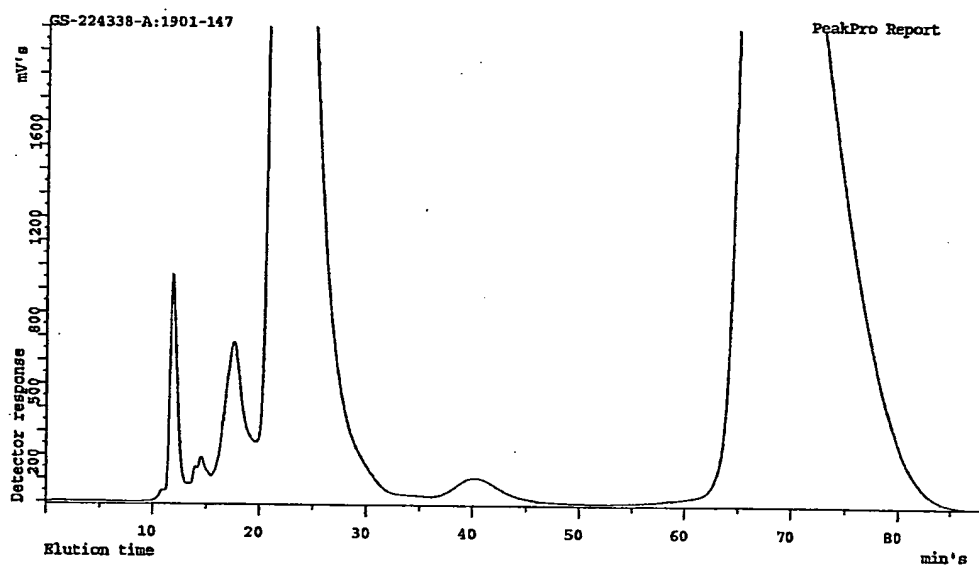
HPLC CONDITIONS

Columns	: Chiralcel OD, 20 μm, 21 x 50 mm (guard)
	: Chiralcel OD, 20 μm, 21 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (65:35 initial)
	: Heptane – Ethyl Alcohol (50:50 intermediate)
	Note: Intermediate began after minor diastereomer peak eluted
	: Heptane – Ethyl Alcohol (20:80 final)
	Note: Final mobile phase began after major diastereomer began to elute
Flow Rate	: 10.0 mL/min
Run Time	: As needed
Detection	: UV at 260 nm
Temperature	: Ambient
Injection	: ~ 300 mg on Column
Sample Prep.	: Dissolved in ~ 3.5 mL hetpane – ethyl alcohol (70:30)
Retention Times	: 35 Minor ~ 14 min
	: 35 Major ~ 40 min
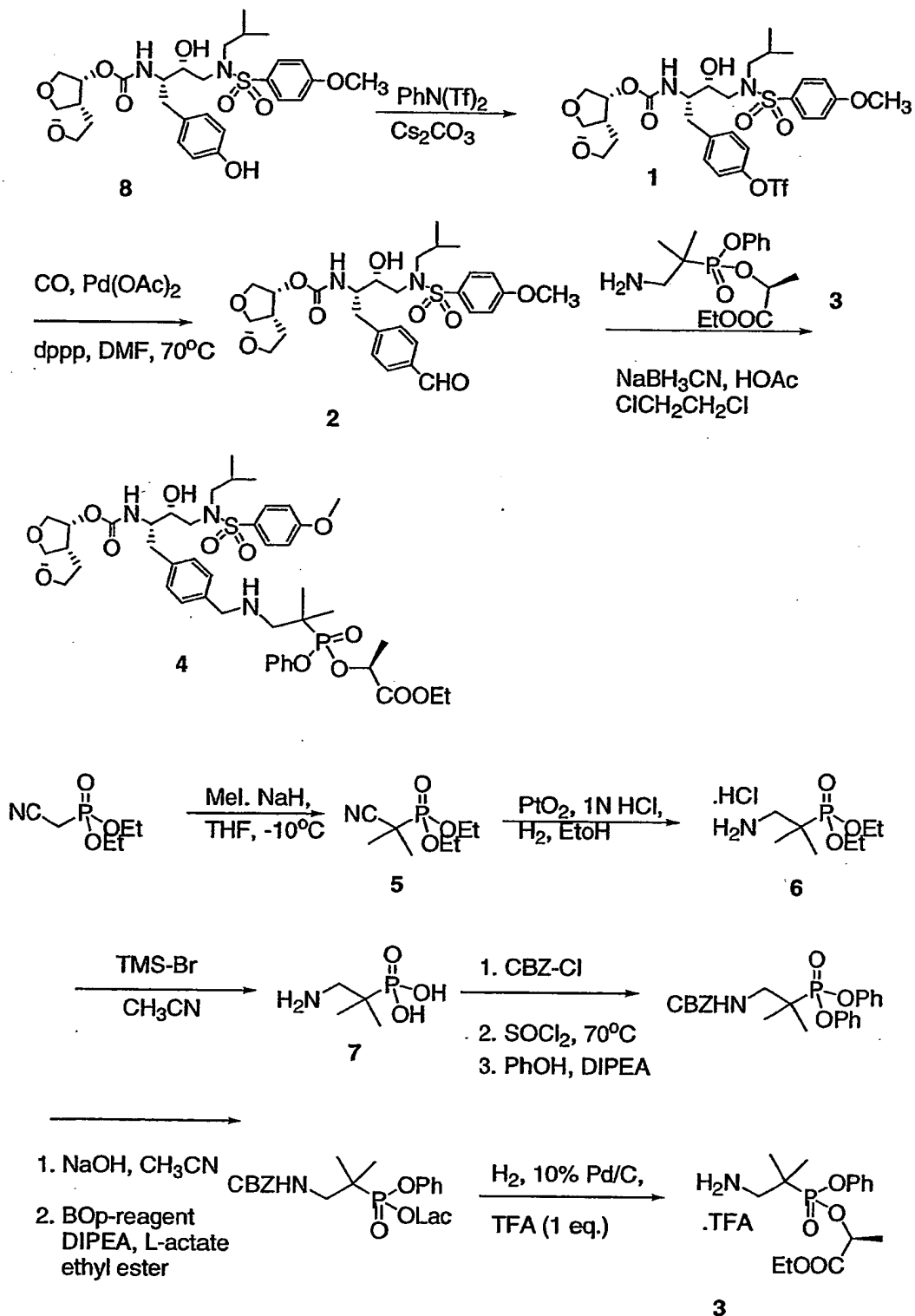
Example 29

Triflate derivative 1: A THF-CH2Cl2 solution (30mL-10 mL) of 8 (4 g, 6.9 mmol), cesium
carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was
reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give
5   crude triflate derivative 1.

Aldehyde 2: Crude triflate 1 (4.5 g, 6.9 mmol) was dissolved in DMF (20 mL), and the
solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)2 (0.12 g,
0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added, the
10   solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution,
then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4
mL, 38 mmol), and triethylsilane (3 ml), 18 mmol). The resulting solution was stirred
overnight at room temperature. The reaction mixture was worked up, and purified on silica
gel column chromatograph to afford aldehyde 2 (2.1 g, 51 %). (Hostetler, et al J. Org. Chem.,
15   1999. 64, 178-185).

Lactate prodrug 4: Compound 4 is prepared as described above procedure for Example 9E,
Compound 35 by the reductive amination between 2 and 3 with NaBH3CN in 1,2-
dichloroethane in the presence of HOAc.
20

Example 30 Preparation of Compound 3

Diethyl (cyano(dimethyl)methyl) phosphonate 5: A THF solution (30 mL) of NaH (3.4 g of
60% oil dispersion, 85 mmol) was cooled to −10°C, followed by the addition of diethyl
(cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The
25   resulting solution was stirred at −10°C for 2 hr, then 0°C for 1 hr, was worked up, and
purified to give dimethyl derivative 5 (5 g, 86 %).

Dietyl (2-amino-1,1-dimethyl-ethyl)phosphonate 6: Compound 5 was reduced to amine
derivative 6 by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

A solution of ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7
30   mmol) was hydrogenated at 1 atmosphere in the presence of PtO2 (1.25 g) at room
temperature overnight. The catalyst was filtered through a celite pad. The filtrate was
concentrated to dryness, to give crude 6 (2.5g, as HCl salt).

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2-Amino-1,1-dimethyl-ethyl phosphonic acid 7: A solution of CH₃CN (30 mL) of crude 6
(2.5 g) was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction
mixture was stirred with methanol for 1.5 hr at room temperature, concentrated, recharged
with methanol, concentrated to dryness to give crude 7 which was used for next reaction
5   without further purification.

Lactate phenyl (2-amino-1,1-dimethyl-ethyl)phosphonate 3: Compound 3 is synthesized
according to the procedures described in Example 9D, Compound 34 for the preparation of
lactate phenyl 2-aminoethyl phosphonate 34. Compound 7 is protected with CBZ, followed
10   by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted
phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-
lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonate derivative. Hydrogenation of
N-CBZ derivative at 1 atmosphere in the presence of 10 % Pd/C and 1 eq. of TFA affords
compound 3 as TFA salt.

Scheme 1
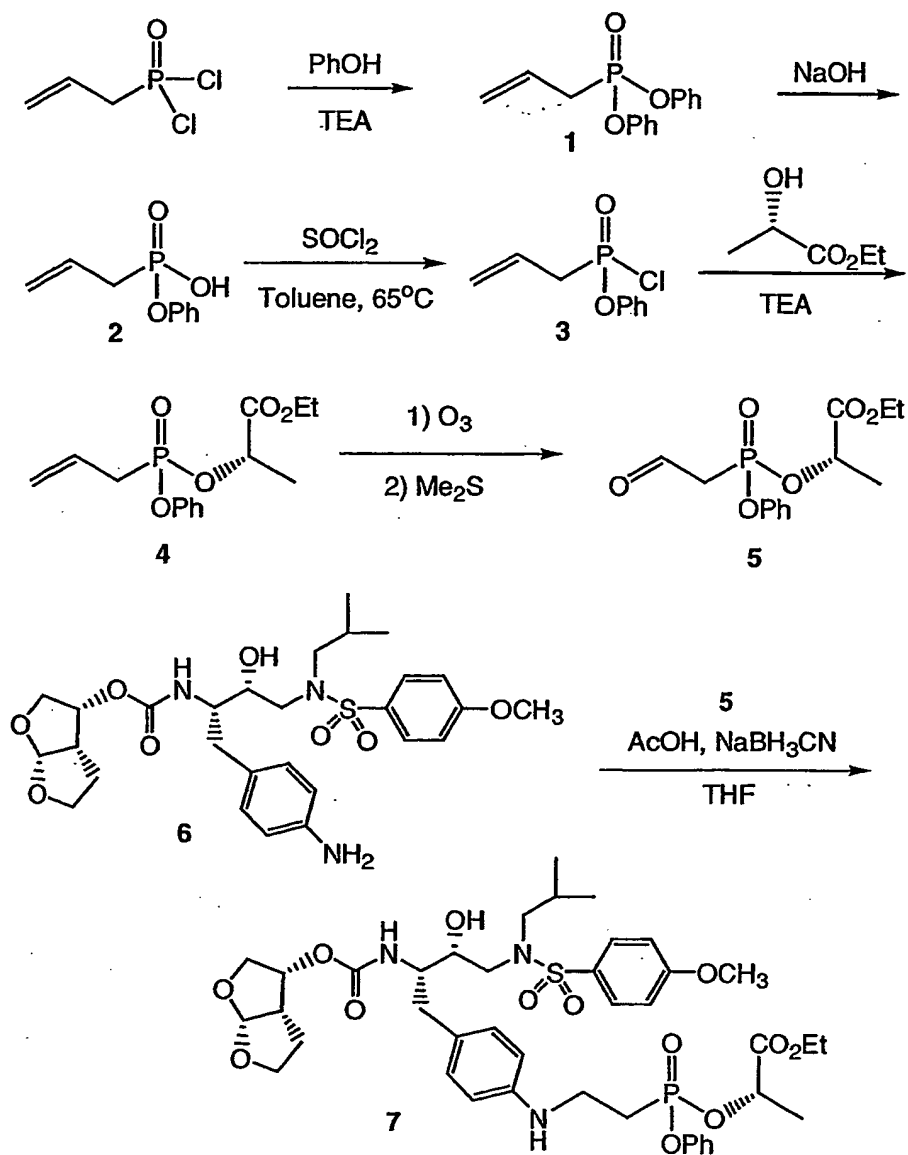
5   <u>Example 1</u>

Monophenol Allylphosphonate 2: To a solution of allylphosphonic dichloride (4 g, 25.4

mmol) and phenol (5.2 g, 55.3 mmol) in CH_2Cl_2 (40 mL) at 0°C was added TEA (8.4 mL, 60

mmol). After stirred at room temperature for 1.5 h, the mixture was diluted with hexane-

ethyl acetate and washed with HCl (0.3 N) and water. The organic phase was dried over

10   MgSO$_4$, filtered and concentrated under reduced pressure. The residue was filtered through a

pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product diphenol

allylphosphonate 1 (7.8 g, containing the excessive phenol) as an oil which was used directly
without any further purification. The crude material was dissolved in CH₃CN (60 mL), and
NaOH (4.4N, 15 mL) was added at 0°C. The resulted mixture was stirred at room
temperature for 3 h, then neutralized with acetic acid to pH = 8 and concentrated under
5   reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50
mL) and washed with CH₂Cl₂ (3X25 mL). The aqueous phase was acidified with
concentrated HCl at 0°C and extracted with ethyl acetate. The organic phase was dried over
MgSO₄, filtered, evaporated and co-evaporated with toluene under reduced pressure to yield
desired monophenol allylphosphonate 2 (4.75 g. 95%) as an oil.

10

Example 2

Monolactate Allylphosphonate 4: To a solution of monophenol allylphosphonate 2 (4.75 g,
24 mmol) in toluene (30 mL) was added SOCl₂ (5 mL, 68 mmol) and DMF (0.05 mL). After
stirred at 65°C for 4 h , the reaction was completed as shown by ³¹P NMR. The reaction
15   mixture was evaporated and co-evaporated with toluene under reduced pressure to give mono
chloride 3 (5.5 g) as an oil. To a solution of chloride 3 in CH₂Cl₂ (25 mL) at 0°C was added
ethyl (s)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at 0°C for 5
min then at room temperature for 1 h, and concentrated under reduced pressure. The residue
was partitioned between ethyl acetate and HCl (0.2N), the organic phase was washed with
20   water, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was
purified by chromatography on silica gel to afford desired monolactate 4 (5.75 g, 80%) as an
oil (2:1 mixture of two isomers): ¹H NMR (CDCl₃) δ 7.1-7.4 (m, 5H), 5.9 (m, 1H), 5.3 (m,
2H), 5.0 (m, 1H), 4.2 (m, 2H), 2.9 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H); ³¹P NMR (CDCl₃)
δ 25.4, 23.9.

25

Example 3

Aldehyde 5: A solution of allylphosphonate 4 (2.5 g, 8.38 mmol) in CH₂Cl₂ (30 mL) was
bubbled with ozone air at −78°C until the solution became blue, then bubbled with nitrogen
until the blue color disappeared. Methyl sulfide (3 mL) was added at −78°C. The mixture
30   was warmed up to room temperature, stirred for 16 h and concentrated under reduced
pressure to give desired aldehyde 5 (3.2 g, as a 1:1 mixture of DMSO): ¹H NMR (CDCl₃) δ
9.8 (m, 1H), 7.1-7.4 (m, 5H), 5.0 (m, 1H), 4.2 (m, 2H), 3.4 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m,
3H); ³¹P NMR (CDCl₃) δ 17.7, 15.4.

Example 4

Compound 7: To a solution of aniline 6 (reported before) (1.62 g, 2.81 mmol) in THF (40
mL) was added acetic acid (0.8 mL, 14 mmol), followed by aldehyde 5 (1.3 g, 80%, 3.46
5   mmol) and MgSO$_4$ (3 g). The mixture was stirred at room temperature for 0.5 h, then
NaBH$_3$CN (0.4 g, 6.37 mmol) was added. After stirred for 1 h, the reaction mixture was
filtered. The filtrate was diluted with ethyl acetate and washed with NaHCO$_3$, dried over
MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by
chromatography on silica gel to give compound 6 (1.1g, 45%) as a 3:2 mixture of two
10   isomers, which were separated by HPLC (mobile phase, 70% CH$_3$CN/H$_2$O; flow rate: 70
mL/min; detection: 254 nm; column: 8μ C18, 41X250 mm, Varian). Isomer A (0.39 g): ^{1}H
NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05
(m, 2H), 4.9 (d, 1H), 4.3 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H),
2.3 (m, 2), 1.6-1.9 (m, 5H), 1.25 (t, 3H), 0.9 (2d, 6H); ^{31}P NMR (CDCl$_3$) δ 26.5; MS (ESI):
15   862 (M+H). Isomer B (0.59 g): ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m,
4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.5 (brs, 1H), 4.2 (q, 2H), 3.5-4.0
(m, 6H), 3.9 (s, 3H), 2.7-3.2 (m, 9H), 2.4 (m, 2), 1.6-1.9 (m, 2H), 1.4 (d, 3H), 1.25 (t, 3H),
0.9 (2d, 6H); ^{31}P NMR (CDCl$_3$) δ 28.4; MS (ESI): 862 (M+H).

Scheme 2
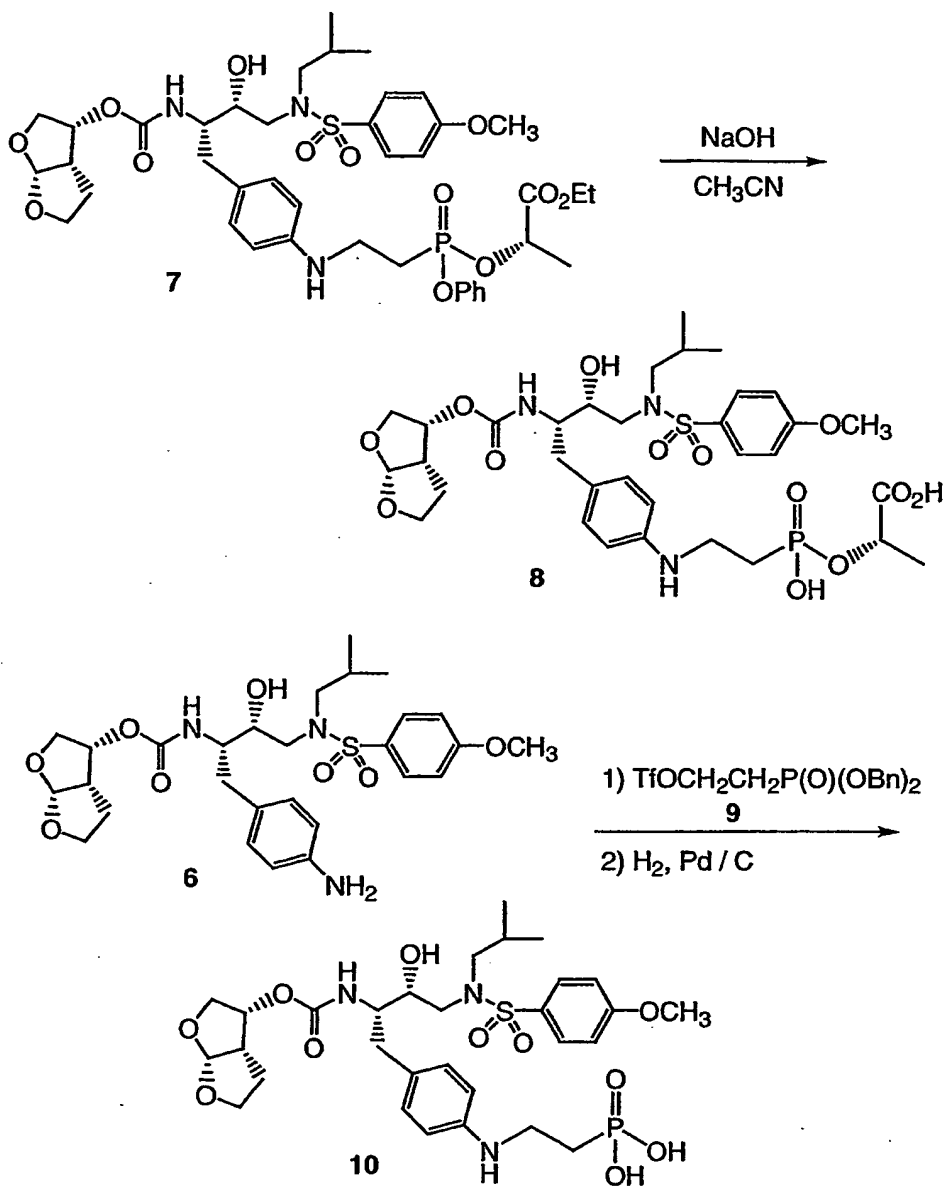
Example 5

5   Acid **8**: To a solution of compound **7** (25 mg, 0.029 mmol) in acetonitrile (1 mL) at 0°C was
added NaOH (1N, 0.125 mL). The mixture was stirred at 0°C for 0.5 h and at room
temperature for 1 h. The reaction was quenched with acetic acid and purified by HPLC to
give acid **8** (10 mg, 45%). ^{1}H NMR (CD$_3$OD) δ 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (d, 2H), 7.1 (d,
2H), 5.6 (d, 1H), 4.9 (m, 3H), 3.2-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.05 (m, 2), 1.4-
10   1.7 (m, 2H), 1.5 (d, 3H), 0.9 (2d, 6H); ^{31}P NMR (CD$_3$OD) δ 20.6; MS (ESI): 758 (M+H).

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Example 6

Diacid **10**: To a solution of triflate **9** (94 mg, 0.214 mmol) in CH$_2$Cl$_2$ (2 mL) was added a solution of aniline 6 (100 mg, 0.173 mmol) in CH$_2$Cl$_2$ (2 mL) at –40°C, followed by 2,6-

5   lutidine (0.026 mL). The mixture was warmed up to room temperature and stirred for 1 h. Cesium carbonate (60 mg) was added and the reaction mixture was stirred for additional 1 h. The mixture was diluted with ethyl acetate, washed with HCl (0.2N), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by HPLC to afford dibenzyl phosphonate (40 mg). To a solution of this dibenzyl phosphonate in ethanol

10   (3 mL) and ethyl acetate (1 mL) was added 10% Pd/C (40 mg). The mixture was stirred under hydrogen atmosphere (balloon) for 4 h. The reaction mixture was diluted with methanol, filtered and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to give desired product diacid **10** (20 mg). ^{1}H NMR (CD$_3$OD) δ 7.8 (d, 2H), 7.3 (d, 2H), 7.1 (2d, 4H), 5.6 (d, 1H), 4.9 (m, 2H), 3.4-4.0 (m, 6H), 3.9 (s, 3H), 2.5-

15   3.2 (m, 9H), 2.0 (m, 2), 1.4-1.7 (m, 2H), 0.9 (2d, 6H); ^{31}P NMR (CD$_3$OD) δ 22.1; MS (ESI): 686 (M+H).

Scheme 3
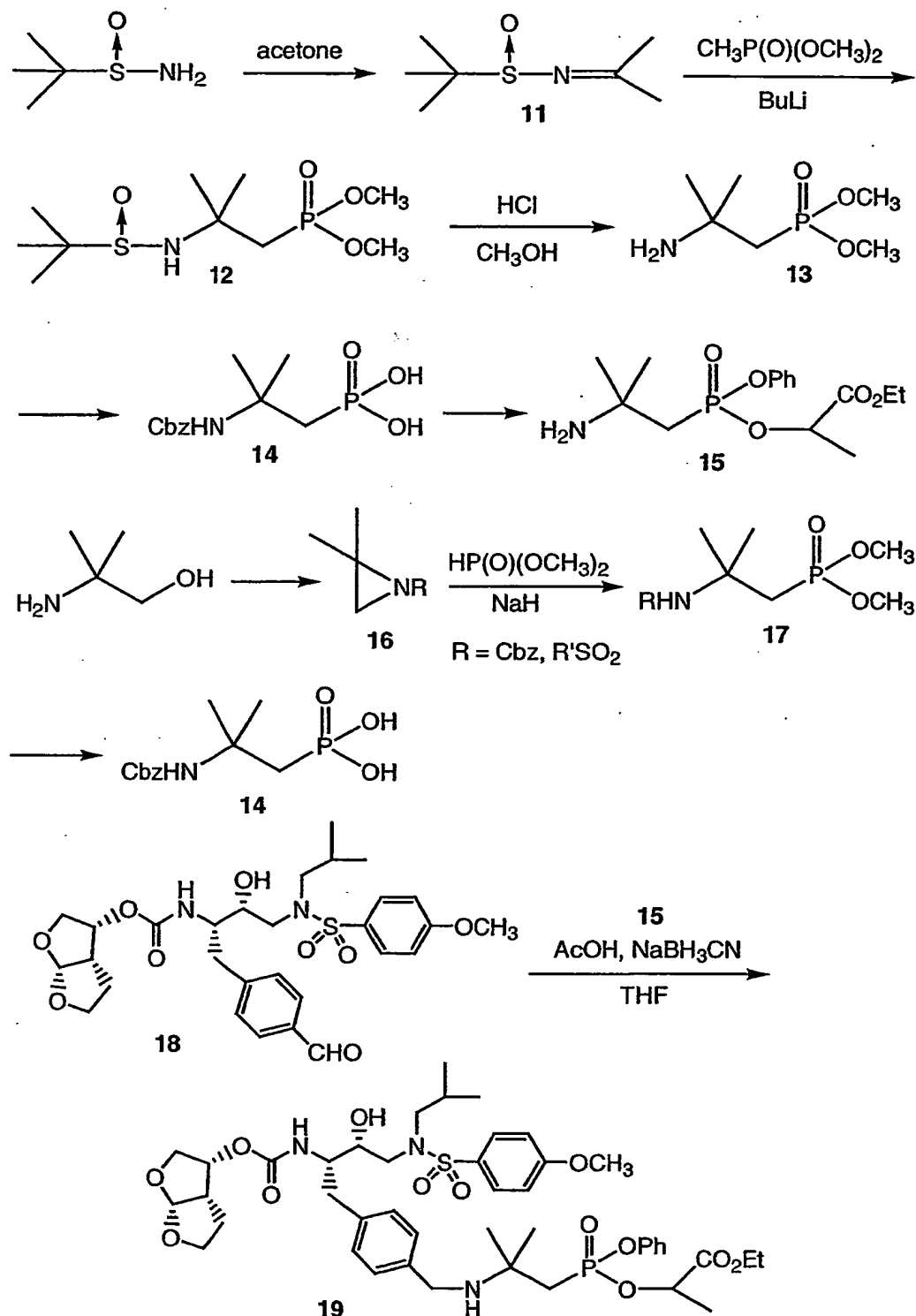
The synthesis of compound **19** is outlined in Scheme 3. Condensation of 2-methyl-2-propanesulfinamide with acetone give sulfinyl imine **11** (J. Org. Chem. 1999, 64, 12).

Addition of dimethyl methylphosphonate lithium to **11** afford **12**. Acidic methanolysis of **12** provide amine **13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid **14**, which can be converted to desired **15** using methods reported earlier on. An alternative synthesis of compound **14** is also shown in Scheme 3. Commercially available

5   2-amino-2-methyl-1-propanol is converted to aziridines **16** according to literature methods (J. Org. Chem. 1992, 57, 5813; and Syn. Lett. 1997, 8, 893). Aziridine opening with phosphite give **17** (Tetrahedron Lett. 1980, 21, 1623). Deprotection (and, if necessary, reprotection) of **17** afford **14**. Reductive amination of amine **15** and aldehyde **18** provides compound **19**.
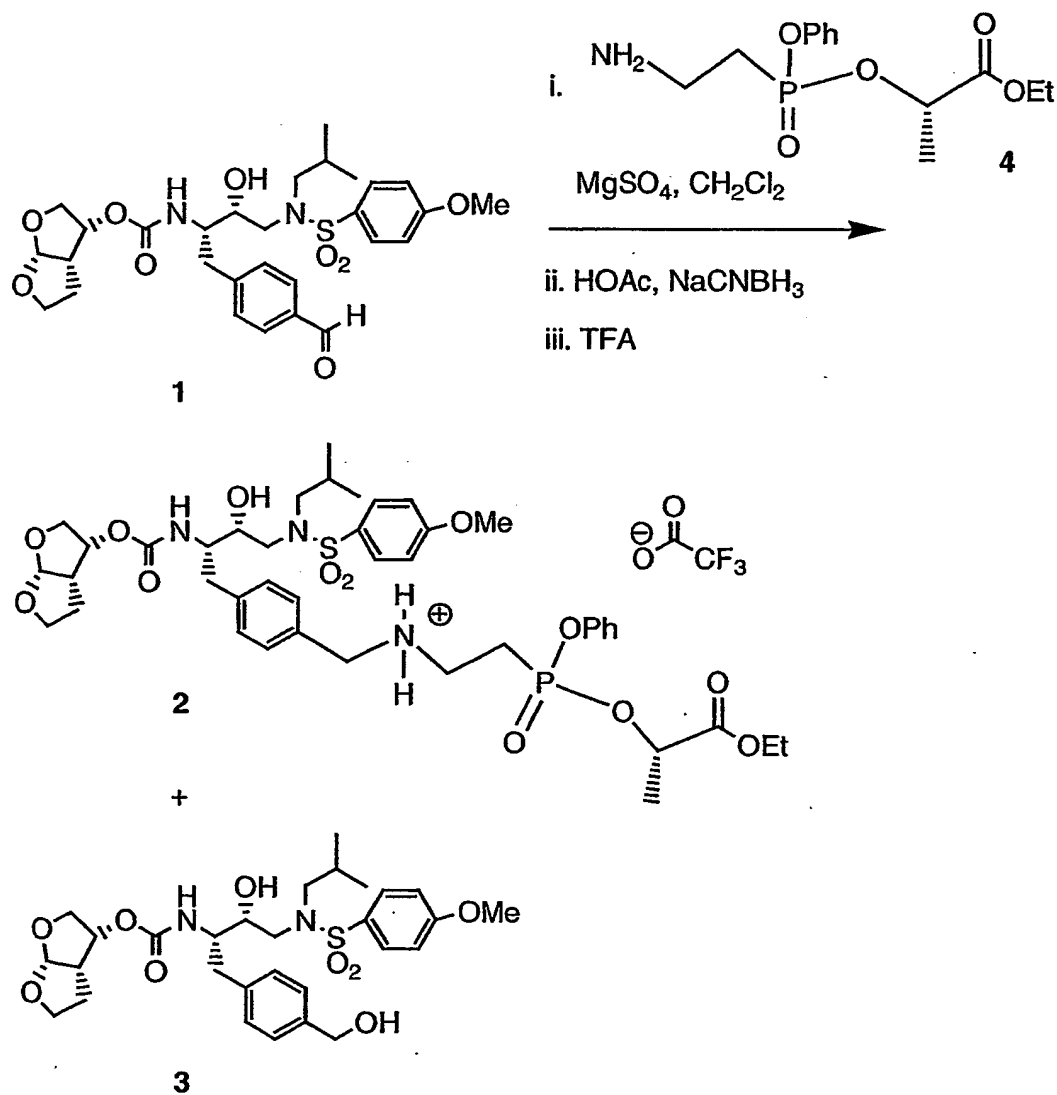
Example 1

2-{[2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester **2** (Compound 35, previous Example 9E).

5

A solution of **1** (2.07 g, 3.51 mmol) and **4** (1.33 g, 3.68 mmol of a 4:1 mixture of two diastereomers at the phosphorous center) were dissolved in 14 mL of (CH₂Cl₂)₂ to provide a clear solution. Addition of MgSO₄ (100 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.80

10   mL, 14.0 mmol) and sodium cyanoborohydride (441 mg, 7.01 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1 hour. The reaction mixture was worked up by addition of 200 mL of saturated aqueous NaHCO₃ and 400 mL of CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ two more times (2 x 300 mL). The combined organic extracts were dried *in vacuo* and purified

15   by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized as alcohol **3** (810 mg, 39%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyopholized from 50 mL of a 1:1 CH₃CN: H₂O to provide 1.63 g (47%) of the product **2** as a white powder. ^{1}H NMR (CD₃CN) δ 8.23 (br s, 2H), 7.79 (d, *J*= 8.4 Hz, 2H), 7.45- 7.13 (m,

20   9H), 7.09 (d, *J*= 8.4 Hz, 2H), 5.86 (d, *J*= 9.0 Hz, 1H), 5.55 (d, *J*= 4.8 Hz, 1H), 5.05-4.96 (m, 1H), 4.96- 4.88 (m, 1H), 4.30-4.15 (m, 4H), 3.89 (s, 3H), 3.86- 3.76 (m, 4H), 3.70- 3.59 (m, 4H), 3.56- 3.40 (m, 2H), 3.34 (d, *J*= 15 Hz, 1H), 3.13 (d, *J*= 13.5 Hz, 1H), 3.06- 2.93 (m, 2H), 2.92- 2.80 (m, 2H), 2.69- 2.43 (m, 3H), 2.03- 1.86 (m, 1H), 1.64- 1.48 (m, 1H), 1.53 and 1.40 (d, *J*= 6.3 Hz, *J*= 6.6 Hz, 3H), 1.45- 1.35 (m, 1H), 1.27 and 1.23 (t, *J*= 6.9 Hz, *J*= 7.2

25   Hz, 3H), 0.90 (t, *J*= 6.9 Hz, 6H). ^{31}P NMR (CD₃CN) δ 24.47, 22.86. ESI (M+ H)$^+$ 876.4.
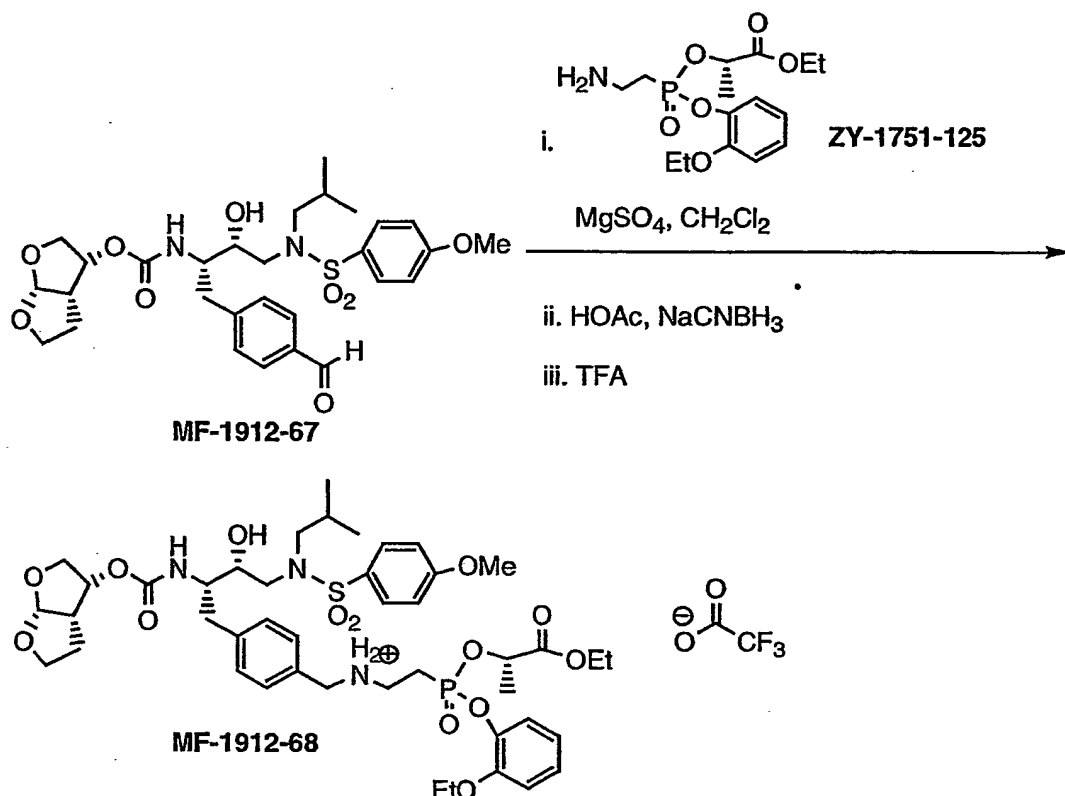
Example 2

MF-1912-67

ZY-1751-125

MgSO$_4$, CH$_2$Cl$_2$

ii. HOAc, NaCNBH$_3$

iii. TFA

MF-1912-68

2-{[2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester (**MF-1912-68**):

A solution of **MF-1912-67** (0.466 g, 0.789 mmol) and **ZY-1751-125** (0.320 g, 0.789 mmol of a 1:1 mixture of two diastereomers at the phosphorous center) were dissolved in 3.1 mL of (CH$_2$Cl$_2$)$_2$ to provide a clear solution. Addition of MgSO$_4$ (20 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.181 mL, 3.16 mmol) and sodium cyanoborohydride (99 mg, 1.58 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1.5 hour. The reaction mixture was worked up by addition of 50 mL of saturated aqueous NaHCO$_3$ and 200 mL of CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$ two more times (2 x 200 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized to be MF-1912-48b alcohol (190 mg, 41%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyopholized from 50 mL of a 1:1 CH$_3$CN: H$_2$O to

provide 0.389 g (48%) of the product as a white powder. ^{1}H NMR (CD3CN) δ 8.39 (br s, 2H), 7.79 (d, *J*= 8.7 Hz, 2H), 7.40 (d, *J*= 7.5 Hz, 2H), 7.34 (d, *J*= 8.1 Hz, 2H), 7.26-7.16 (m, 2H), 7.10 (d, *J*= 9 Hz, 3H), 7.01- 6.92 (m, 1H), 5.78 (d, *J*= 9.0 Hz, 1H), 5.55 (d, *J*= 5.1 Hz, 1H), 5.25-5.03 (m, 1H), 4.95- 4.88 (m, 1H), 4.30- 4.17 (m, 4H),4.16- 4.07 (m, 2H), 3.90 (s, 3H), 3.88-3.73 (m, 4H), 3.72- 3.60 (m, 2H), 3.57- 3.38 (m, 2H), 3.32 (br d, *J*= 15.3 Hz, 1H), 3.13 (br d, *J*= 14.7 Hz, 1H), 3.05- 2.92 (m, 2H), 2.92- 2.78 (m, 2H), 2.68- 2.48 (m, 3H), 2.03-1.90 (m, 1H), 1.62- 1.51 (m, 1H), 1.57 and 1.46 (d, *J*= 6.9 Hz, *J*= 6.9 Hz, 3H), 1.36- 1.50 (m, 1H), 1.43- 1.35 (m, 4H), 1.33- 1.22 (m, 3H), 0.91 (t, *J*= 6.6 Hz, 6H). ^{31}P NMR (CD$_3$CN) δ 25.27, 23.56. ESI (M+ H)$^+$ 920.5.

Scheme 1

Scheme 2

4 + 5

6

7

8
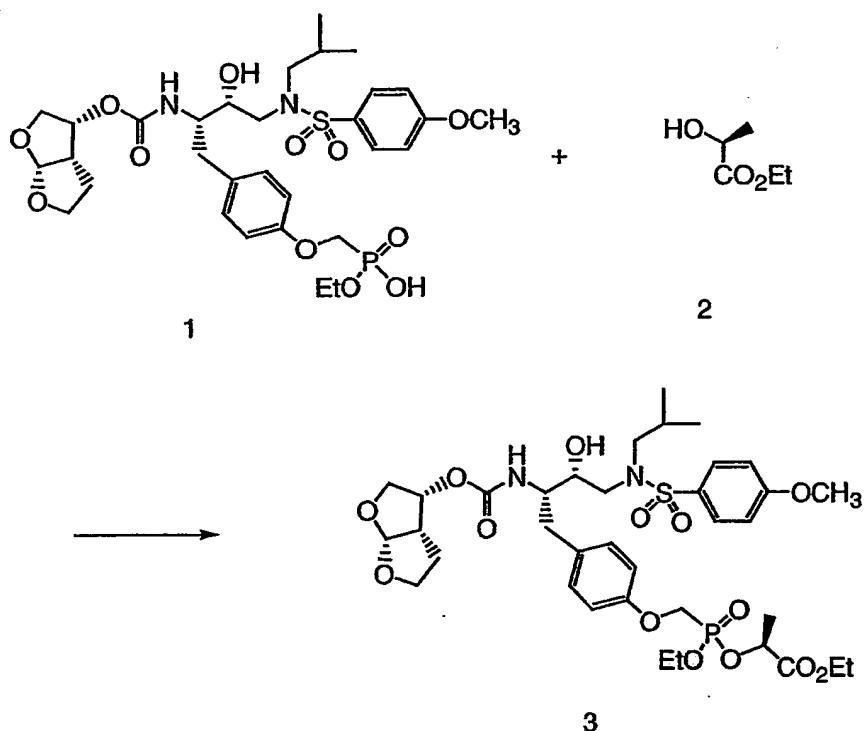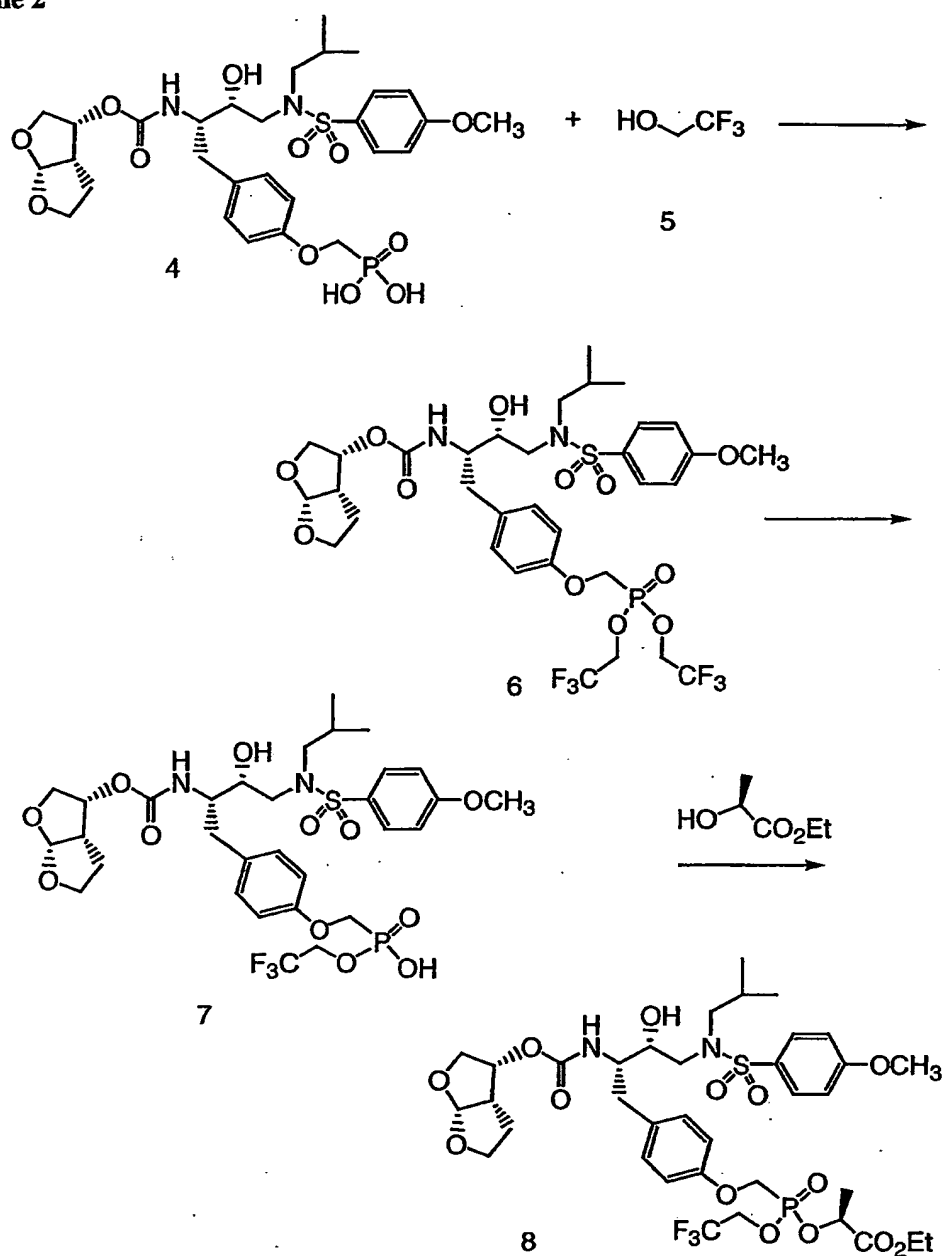
Example 1

5   Mono-Ethyl mono-lactate 3: To a solution of 1 (96mg, 0.137 mmol) and ethyl lactate 2 (0.31

mL, 2.7 mmol) in pyridine (2 mL) was added N, N-dicyclohexylcarbodiimide (170 mg, 0.822

mmol). The solution was stirred for 18h at 70°C. The mixture was cooled to room

temperature and diluted with dichloromethane. The solid was removed by filtration and the

filtrate was concentrated. The residue was suspended in diethyl ether/dichloromethane and

filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 3 (43 mg, 40%) as a foam: ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.00 (d, 2H); 7.00 (d, 2H), 6.88 (d, 2H), 5.67 (d, 1H), 4.93-5.07 (m, 2H), 4.15-4.39 (m, 6H), 3.70-3.99 (m, 10H), 2.76-3.13 (m, 7H), 1.55-1.85 (m, 9H), 1.23-1.41

5   (m, 6H), 0.90 (dd, 6H); ^{31}P NMR (CDCl$_3$) δ 19.1, 20.2; MS (ESI) 823 (M+Na).

Example 2

Bis-2,2,2-trifluoroethyl phosphonate 6: To a solution of 4 (154mg, 0.228 mmol) and 222,-trifluoroethanol 5 (1 mL, 13.7 mmol) in pyridine (3 mL) was added N, N-

10   dicyclohexylcarbodiimide (283 mg, 1.37 mmol). The solution was stirred for 6.5h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the filtrate was concentrated. The residue was suspended in dichloromethane and filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 6 (133 mg,

15   70%) as a foam: ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.21 (d, 2H); 7.00 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.94-5.10 (m, 3H), 4.39-4.56 (m, 6H), 3.71-4.00 (m, 10H), 2.77-3.18 (m, 7H), 1.67-1.83(m, 2H), 0.91 (dd, 4H); ^{31}P NMR (CDCl$_3$) δ 22.2; MS (ESI) 859 (M+Na).

Example 3

20   Mono-2,2,2-trifluoroethyl phosphonate 7: To a solution of 6 (930mg, 1.11 mmol) in THF (14 mL) and water (10 mL) was added an aqueous solution of NaOH in water (1N, 2.2 mL). The solution was stirred for 1h at 0°C. An excess amount of Dowex resin (H$^+$) was added to until pH=1. The mixture was filtered and the filtrate was concentrated under reduced pressure. The concentrated solution was azeotroped with EtOAc/toluene three times and the white

25   powder was dried *in vacuo* provide compound 7 (830 mg, 100%). ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.11 (d, 2H); 6.99 (d, 2H), 6.85 (d, 2H), 5.63 (d, 1H), 5.26 (m, 1H), 5.02 (m, 1H), 4.40 (m, 1H), 4.14 (m, 4H), 3.60-3.95 (m, 12H), 2.62-3.15 (m, 15H), 1.45-1.84 (m, 3H), 1.29 (m, 4H), 0.89 (d, 6H); ^{31}P NMR (CDCl$_3$) δ 19.9; MS (ESI) 723 (M+Na).

30   Example 4

Mono-2,2,2-trifluoroethyl mono-lactate 8: To a solution of 7 (754mg, 1 mmol) and N, N-dicyclohexylcarbodiimide (1.237 g, 6 mmol) in pyridine (10 mL) was added ethyl lactate

(2.26 mL, 20 mmol). The solution was stirred for 4.5h at 70°C. The mixture was concentrated and the residue was suspended in diethyl ether (5 mL) and dichloromethane (5 mL) and filtered. The solid was washed a few times with diethyl ether. The combined filtrate was concentrated and the crude product was chromatographed on silica gel, eluting

5   with EtOAc and hexane to provide compound 8 (610 mg, 71%) as a foam. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.16 (d, 2H); 6.99 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.95-5.09 (m, 2H), 4.19-4.65 (m, 6H), 3.71-4.00 (m, 9H), 2.76-3.13 (m, 6H), 1.57-1.85 (m, 7H), 1.24-1.34 (m, 4H), 0.91 (dd, 6H); ^{31}P NMR (CDCl$_3$) δ 20.29, 21.58; MS (ESI) 855 (M+1).

10   Example 1

Boc-protected hydroxylamine **1**: A solution of diethyl hydroxymethyl phosphonate triflate (0.582 g, 1.94 mmol) in dichloromethane (19.4 mL) was treated with triethylamine (0.541 mL, 3.88 mmol). Tert-butyl N-hydroxy-carbamate (0.284 g, 2.13 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned

15   between dichloromethane and water. The organic phase was washed with saturated NaCl, dried (MgSO$_4$) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 – ethyl acetate/hexane) affording the BOC-protected hydroxylamine **1** (0.41 g, 75%) as an oil: ^{1}H NMR (CDCl$_3$) δ 7.83 (s, 1H), 4.21 (d, 2H), 4.18 (q, 4H), 1.47 (s, 9H), 1.36 (t, 6H); ^{31}P NMR (CDCl$_3$) δ 19.3.

20

Example 2

Hydroxylamine **2**: A solution of BOC-protected hydroxylamine **1** (0.305 g, 1.08 mmol) in dichloromethane (2.40 mL) was treated with trifluoroacetic acid (0.829 mL, 10.8 mmol). The reaction was stirred for 1.5 hours at room temperature and then the volatiles were evaporated

25   under reduced pressure with toluene to afford the hydroxylamine **2** (0.318 g, 100%) as the TFA salt which was used directly without any further purification: ^{1}H NMR (CDCl$_3$) δ 10.87 (s, 2H), 4.45 (d, 2H), 4.24 (q, 4H), 1.38 (t, 6H); ^{31}P NMR (CDCl$_3$) δ 16.9; MS (ESI) 184 (M+H).

30   Example 3

Oxime **4**: To a solution of aldehyde **3** (96 mg, 0.163 mmol) in 1,2-dichloroethane (0.65 mL) was added hydroxylamine **2** (72.5 mg, 0.244 mmol), triethylamine (22.7 µL, 0.163 mmol) and MgSO$_4$ (10 mg). The reaction mixture was stirred at room temperature for 2 hours then

the mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (90/10 – ethyl acetate/hexane) affording, GS-277771, oxime **4** (0.104 g, 85%) as a solid: ^{1}H NMR (CDCl₃) δ 8.13 (s, 1H),
5   7.72 (d, 2H), 7.51 (d, 2H), 7.27 (d, 2H), 7.00 (d, 2H), 5.67 (d, 1H), 5.02 (m, 2H), 4.54 (d, 2H), 4.21 (m, 4H), 3.92 (m, 1H), 3.89 (s, 3H), 3.88 (m, 1H), 3.97-3.71 (m, 2H), 3.85-3.70 (m, 2H), 3.16-2.99 (m, 2H), 3.16-2.81 (m, 7H), 1.84 (m, 1H), 1.64-1.48 (m, 2H), 1.37 (t, 6H), 0.94-0.90 (dd, 6H); ^{31}P NMR (CDCl₃) δ 20.0; MS (ESI) 756 (M+H).

10   <u>Scheme 1</u>

15
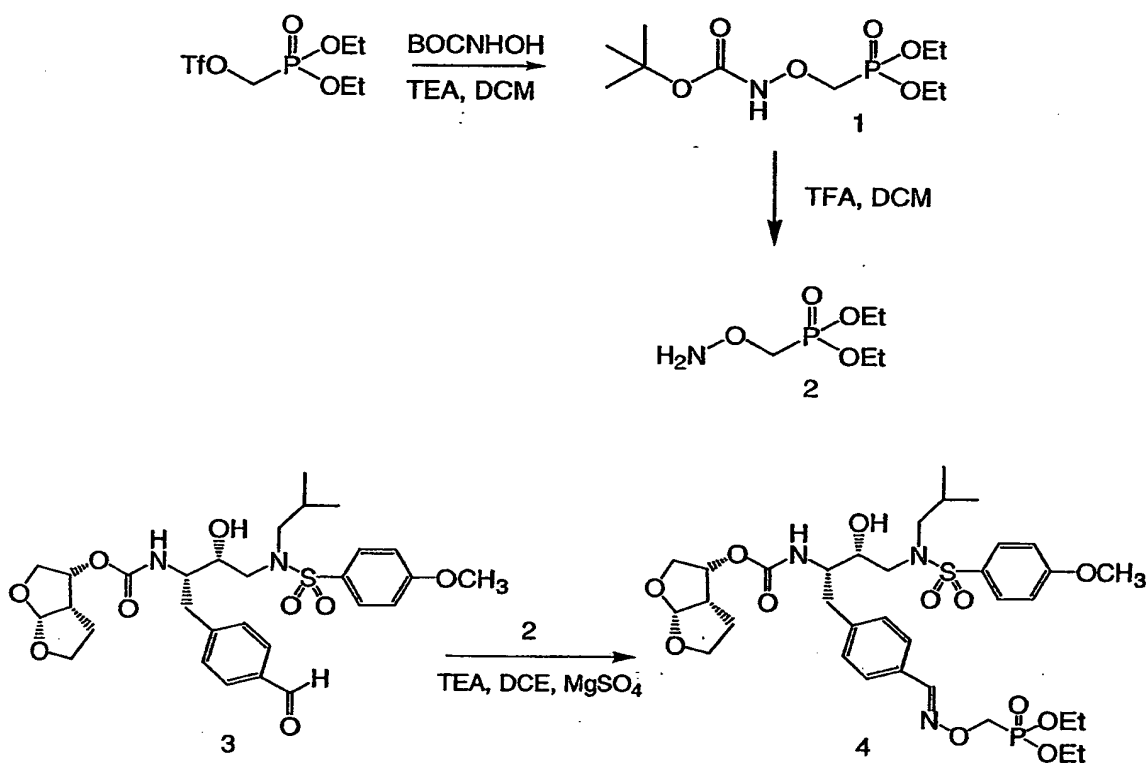
Scheme 1
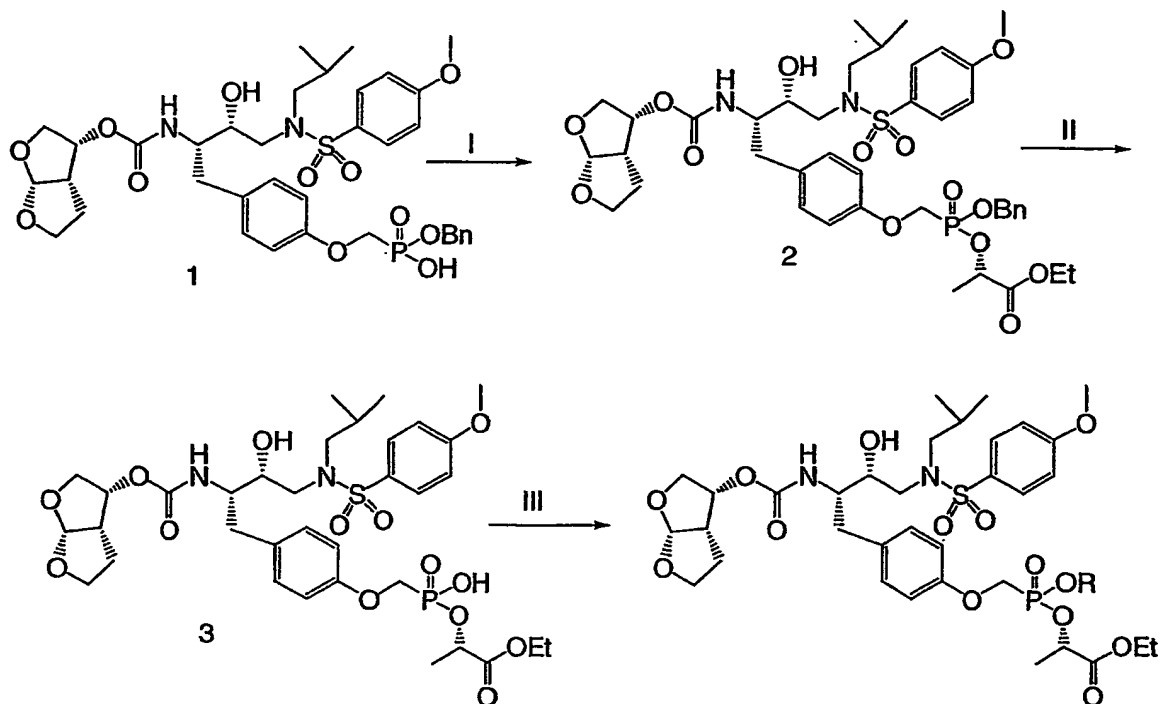
I. Ethyl(S)-(-)lactate/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc; II. H$_2$/20%Pd-C/EtOAc-EtOH; III. ROH/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc
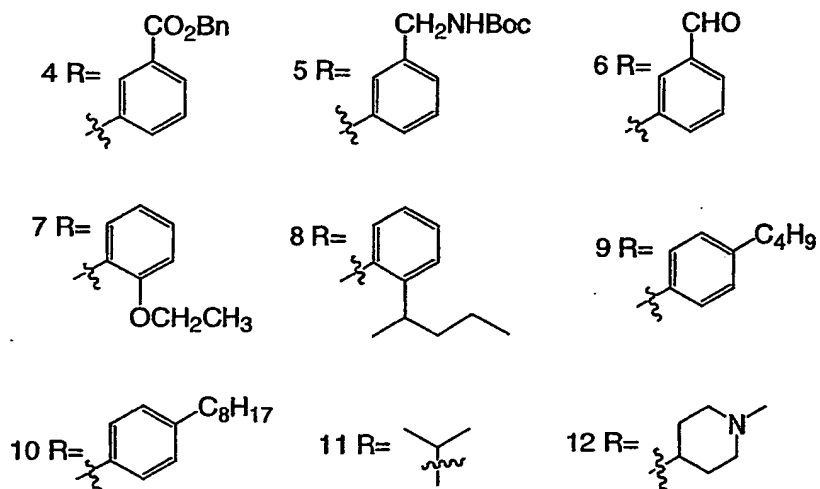
Example 1

Compound 1 was prepared according to methods from previous Schemes

Example 2

5   Compound 2: To a solution of compound 1 (5.50 g, 7.30 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (5.70g, 10.95 mmol), and Ethyl(S)-(-)lactate (1.30 g, 10.95 mmol) in DMF (50 mL) was added Diisopropylethylamine(5.08 mL, 29.2 mmol). The mixture was stirred for 7 hours after which was diluted in EtOAc. The organic phase was washed with H_2O (5X), brine, dried over $MgSO_4$ and *concentrated in*

10   *vacuo.* The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/4) to give 3.45 g of compound 2.

Example 3

Compound 3: To the mixture of compound 2 (3.45 g) in EtOH/EtOAc (300 mL/100 mL) was

15   added 20% Pd/C(0.700 g). The mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 2.61 g of compound 3.

Example 4

20   Compound 4: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (5 mL) was added 3-Hydroxy-benzoic acid benzyl ester (0.589 g, 2.58 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.34 g, 2.58 mmol), followed by addition of Diisopropylethylamine (900 μL, 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over

25   sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/3) to provide 67.3 mg of compound 4: ^{1}H NMR (CDCl₃) δ 7.91 (2H,d, J=8.9 Hz), 7.75 (2H, m), 7.73-7.3 (13H,m), 7.25 (2H, m), 7.21-6.7(6H, m), 5.87(1H, m), 5.4-4.8(6H, m), 4.78-4.21 (4H, m), 3.98 (3H,s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28(3H, m), 0.99(6H, m).

30

Example 5

Compound 5: To a solution of compound 3 (1.40 g, 1.81 mmol) in dry dimethylformamide (5 mL) was added (4-Hydroxy-benzyl)-carbamic acid tert-butyl ester (0.80 g, 3.62 mmol),

Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.74 g, 3.62 mmol),

followed by addition of Diisopropylethylamine (1.17 ml, 7.24 mmol). The mixture was

stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and

dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue

5   was purified by silica gel chromatography (CH$_2$Cl$_2$/Isopropanol= 100/3.5) to provide 770 mg

of compound 5: ^{1}H NMR (CDCl$_3$) δ 7.8(2H, d, J=8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75

(1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (12H, m),

1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

10   Example 6

Compound 6: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide

(6 mL) was added 3-Hydroxybenzaldehyde (0.320 g, 2.60 mmol), Benzotriazol-1-

yloxytripyrrolidinophosphonium hexafluorophosphate (1.35 g, 2.60 mmol), followed by

addition of Diisopropylethylamine (901 μL, 5.16 mmol). The mixture was stirred for 14

15   hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over

sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified

by silica gel chromatography (CH$_2$Cl$_2$/Isopropanol= 100/5) to provide 880 mg of compound

6.

20   Example 7

Compound 7: To a solution of compound 3 (150 mg, 0.190 mmol) in dry

dimethylformamide (1 mL) was added 2-Ethoxy-phenol (48.0 μL, 0.380 mmol),

Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (198 mg, 0.380 mmol),

followed by addition of Diisopropylethylamine (132 μL, 0.760 mmol). The mixture was

25   stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and

dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue

was purified by silica gel chromatography (CH$_2$Cl$_2$/Isopropanol= 100/4) to provide 84.7 mg

of compound 7: ^{1}H NMR (CDCl$_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.15 (2H, m), 7.01-6.9 (8H, m),

5.66 (1H, m), 5.22-5.04 (2H, m), 4.56- 4.2 (6H, m), 4.08 (2H, m), 3.89 (3H, m), 3.85-3.69

30   (6H, m), 3.17-2.98 (7H, m), 2.80(3H, m) 1.86 (1H, m),1.65(2H, m), , 1.62-1.22 (6H, m),

0.92(6H, m).

Example 8

Compound 8: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 2-(1-methylbutyl) phenol (21.2 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0 μL, 0.260 mmol). The mixture

5 was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 8.20 mg of compound 8: ^{1}H NMR (CDCl$_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.25 (2H, m), 7.21-6.89 (8H, m), 5.7(1H, m), 5.29-4.9 (2H, m), 4.56- 4.2 (6H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.89 (8H, m), 2.85(3H, m), 2.3-

10 1.65(4H, m), 1.55-1.35 (6H, m), 0.92(6H, m).

Example 9

Compound 9: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added) 4-N-Butylphenol (19.4 mg, 0.130 mmol),

15 Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition (45.0 μL, 0.260 mmol) of Diisopropylethylamine. The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 9.61 mg of compound 9: ^{1}H NMR (CDCl$_3$)

20 δ 7.8(2H, d, J=8.9 Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-4.5 (4H, m), 4.3-3.4.1 (4H, m), 3.9 (3H, m), 3.3-2.59 (11H, m), 2.25 (2H, m), 1.85-1.5 (5H, m), 1.4-1.1(10H, m), 0.95(9H, m).

Example 10

25 Compound 10: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 4-Octylphenol (26.6 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0 μL, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over

30 sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 7.70 mg of compound 10: ^{1}H NMR (CDCl$_3$) δ 7.75 (2H, d, J=8.9 Hz), 7.3 (2H, m), 7.2-6.8 (8H, m), 5.70 (1H, m), 5.3-4.9 (4H, m), 4.6- 3.9 (4H, m),

3.89 (3H, m), 3.85-2.59 (12H, m), 2.18-1.75 (10H, m), 1.69-1.50 (8H, m), 1.4-1.27(6H,m), 0.95(9H, m).

Example 11

5   Compound 11: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1 mL) was added Isopropanol (20.0 µL, 0.240 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0 µL, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over

10   sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂/Isopropanol= 100/4) to provide 12.2 mg of compound 11: ^{1}H NMR (CDCl₃) δ 7.71 (2H, d, J=8.9 Hz), 7.15 (2H, m), 7.0 (2H, m), 6.89 (2H, m), 5.65 (1H, m), 5.03-4.86(4H, m), 4.34-4.19 (3H, m), 3.89 (3H, s), 3.88 (1H, m), 3.82 (2H, m), 3.65 (4H, m), 3.2-2.9 (11H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m),

15   1.30(3H,m), 0.92(6H, m).

Example 12

Compound 12: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1mL) was added 4-Hyrdroxy-1-methylpiperidine (30.0 mg, 0.240

20   mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0 µL, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 50.1 mg of compound 12: ^{1}H NMR

25   (CDCl₃) δ 7.73 (2H, d, J=8.9 Hz), 7.18 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (14H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

Scheme 2

4   → I

I. H₂/10%Pd-C/EtOAc

Scheme 3

5   → I

I. a:TFA/CH₂Cl₂/0°C; b:HCHO/HOAc/NaBH₃CN/EtOAc/0°C

Scheme 4

6   → I

I. R₂NH /HoAC/NaBH₃CN/EtOAc
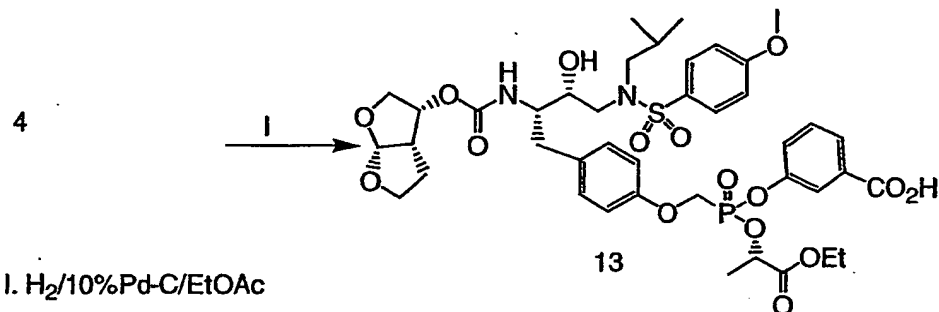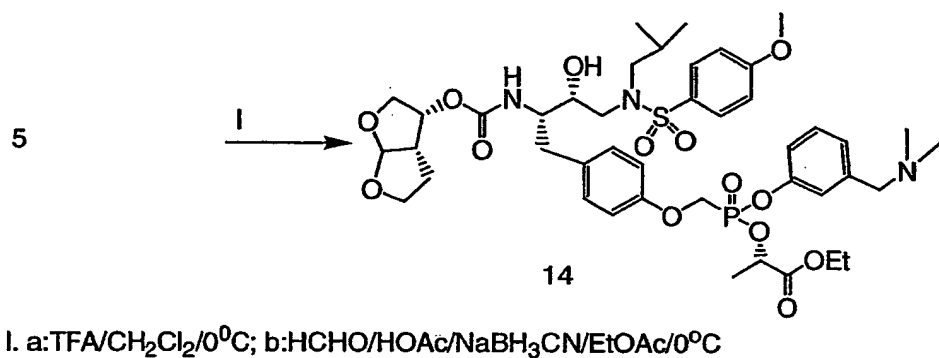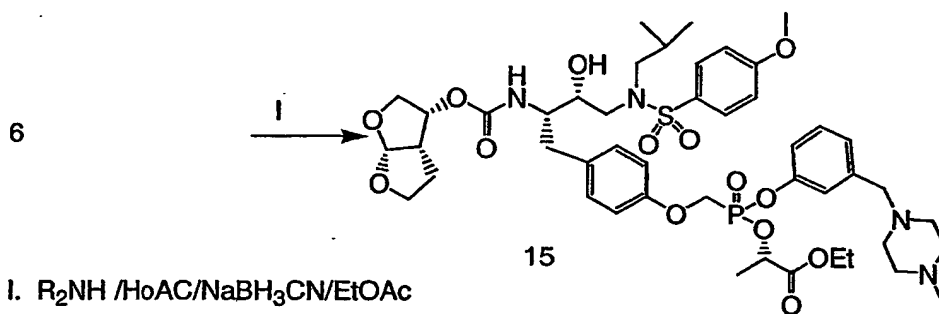
5

Example 13

Compound 13: To a solution of compound 4 (4.9 g)) in EtOAc (150ml) was added 20% Pd/C
(0.90 g),the reaction mixture was hydrogenated for 1 hour. Celite was added and the mixture
was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with

10   ethanol. Concentration gave 4.1 g of compound 13: ^{1}H NMR (CDCl₃) δ 7.91 (2H,d, J=8.9 Hz),

7.75 (2H, m), 7.73-7.3 (8H, m), 7.25 (2H, m), 7.21-6.7(6H, m), 5.4-4.8(6H, m), 4.78-4.21 (4H, m), 3.98 (3H,s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28(3H, m), 0.99(6H, m).

Example 14

5   Compound 14: To a solution of compound 5 (0.770 g, 0.790 mmol) in dichloromethane (10 mL), under ice-cooling, was added triflouroacetic acid (5 mL), the resulting mixture was stirred at 25°C for two hours. The reaction mixture was concentrated under reduced pressure and the residue was co-evaporated with EtOAc to provide an yellow oil. To a solution of the above oil in (10 mL) of EtOAc, under ice-cooling and stirring was added formaldehyde (210

10   µL, 2.86 mmol), acetic acid (252 µL, 4.30 mmol), followed by sodium cyanoborohydride (178 mg, 2.86 mmol). The mixture was further stirred at 25°C for 2 hours. The above mixture was concentrated and diluted with EtOAc and washed with H_2O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using reversed-phase HPLC to provide 420 mg of compound 14: ^{1}H NMR (CDCl_3)

15   δ 7.8(2H, d, J=8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (8H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

Example 15

20   Compound 15: To a solution of compound 6 (100mg, 0.114 mmol) in EtOAc (1 mL) was added 1-Methyl-piperazine (63.2 mg, 0.570 mmol), acetic acid (34.0 µl, 0.570 mmol) followed by Sodium Cyanoborohydride (14.3 mg, 0.228mmol). The mixture was stirred at 25°C for 14 hours. The reaction mixture was concentrated and diluted with EtOAc and washed with H_2O (5X), brine (2x), dried over sodium sulfate, filtered, and concentrated under reduced pressure.

25   The residue was purified using silica gel chromatography (CH_2Cl_2/Isopropanol= 100/6.5) to give 5.22 mg of compound 15: ^{1}H NMR (CDCl_3) δ 7.73 (2H, d, J=8.9 Hz), 7.4-7.18(8H, m), 7.1-6.89 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80-2.25 (8H,m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

Scheme 5

3 —— I ——→

16
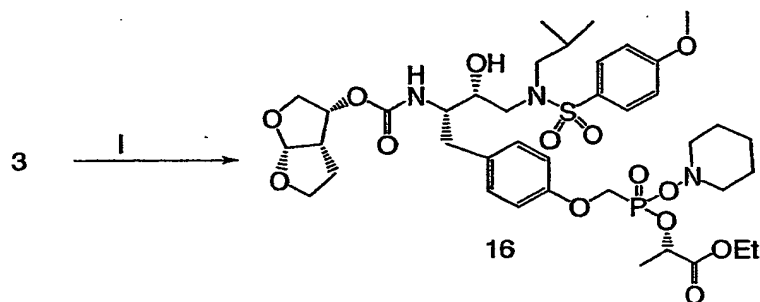
I.Piperidin-1-ol/DCC/Pyridine

Scheme 6

17   I ——→   **18**
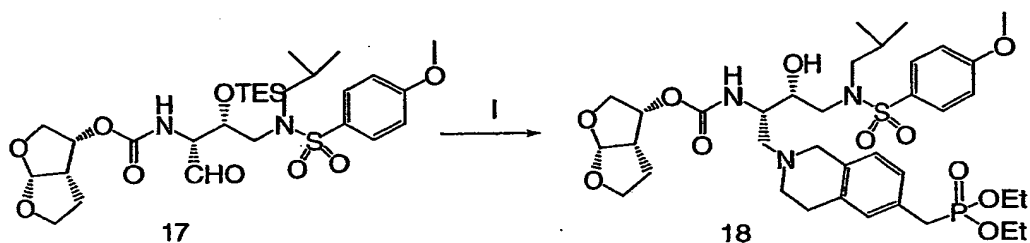
I. a:R₂NH /HOAc/NaBH₃CN/EtOAc b: 2%HF/CH₃CN

Example 16

Compound 16: To a solution of compound 3 (100mg, 0.120 mmol) in Pyridine (600 µL) was
added Piperidin-1-ol (48.5 mg, 0.480 mmol), followed by N,N-Dicyclohexylcarbodiimide
(99.0 mg, 0.480 mmol). The mixture was stirred for 6 hours, the solvent was concentrated
under reduced pressure. The resulting residue was purified by silica gel chromatography
(CH₂Cl₂/Methanol= 100/5) to provide 17 mg of compound 16: ¹H NMR (CDCl₃) δ 7.73 (2H,
d, J=8.9 Hz), 7.16 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.68 (1H, m), 5.17 (1H, m), 5.04 (1H,
m), 4.5-4.2 (4H, m), 3.90 (3H, s), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80(3H,
m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.5-1.27 (9H,m), 0.92(6H, m).

Example 17

Compound 18: To a solution of compound 17 (148 mg, 0.240 mmol) in 4 mL of Methanol was added (1,2,3,4-Tetrahydro-isoquinolin-6-ylmethyl)-phosphonic acid diethyl ester (70.0 mg, 0.240 mmol), acetic acid (43.0 µL, 0.720 mmol). The reaction mixture was stirred for 3

5   minutes, followed by addition of Sodium Cyanoborohydride (75.3 mg, 1.20 mmol). The reaction mixture was stirred at 25°C for 14 hours. The reaction mixture was diluted with EtOAc and washed with H2O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH2Cl2/Isopropanol= 100/5) to give 59 mg of TES·protected intermediate.

10   83 µL of 48% HF solution was added to acetonitrile (4 mL) to prepare the 2% HF solution. The above 2% HF solution was added to TES protected intermediate (47 mg, 0.053 mmol) and the reaction mixture was stirred for 2 hours. The solvent was concentrated and the residue was diluted with EtOAc, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography

15   (CH2Cl2/Methanol= 100/10) to give 35.2 mg of compound 18: ^{1}H NMR (CDCl3) δ 7.73 (2H, d, J=8.9 Hz), 7.05 (2H, m), 6.89 (2H, m), 6.76 (1H, m), 5.75 (1H, m), 5.67 (1H, m), 5.3 (2H, m), 4.2-3.6 (12 H, m), 3.4-2.4 (11 H, m), 2.1-1.8 (6H, m), 1.4-1.28 (8 H, m), 0.92(6H, m).

Scheme 7

R$_1$ = Me, Et, i-Pr
R$_2$ = Me, Et, i-Pr

I. Isopropanol/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/DMF;
II. H$_2$/10%Pd-C/EtOAc-EtOH;
III. RNH$_2$/Aldrithiol-2/PPh$_3$/iPr$_2$NEt/pyridine
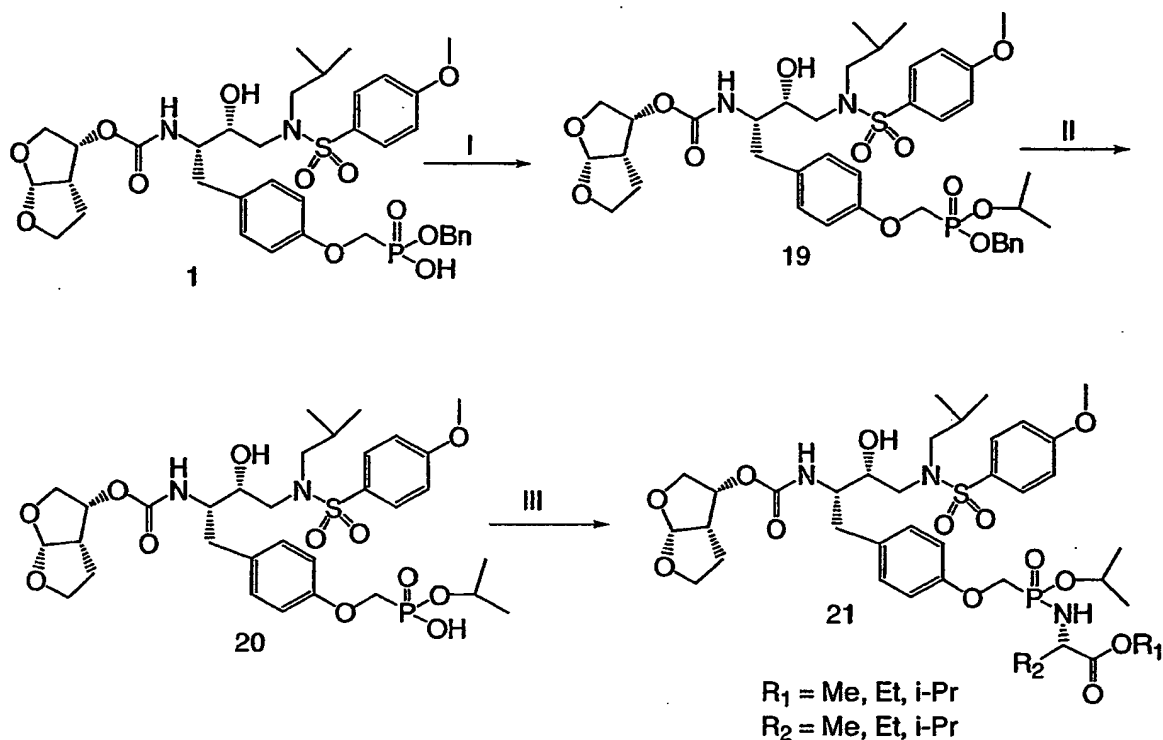
Compound 19 is prepared following the procedure for compound 2 by using monoacid 1.

5   Compound 20 is made following a hydrogenation of compound 19. Mono acid 20 reacts with corresponding amino esters in the presence of Aldrithiol-2 and triphenylphosphine to form compound 21.

Scheme 8
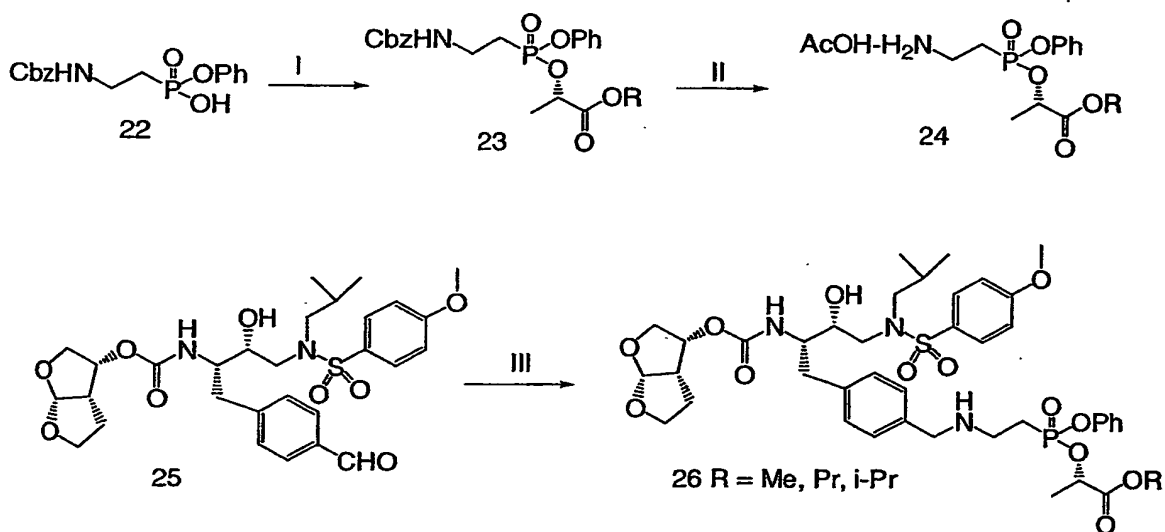
I. a. SOCl₂/60 C; b. Alkyl (s)-lactate/Et₃N; II. H₂/10%Pd-C/EtOAc-HOAc;
III. a. compound 25/MgSO₄;b. HOAc/NaBH₃CN

Monoacid 22 is treated with thionyl chloride at 60°C to form monochloridate, which reacts
with corresponding alkyl (s)lactate to generate monolactate 23. Monolactate 23 is
hydrogenated with 10%Pd-C in the presence of acetic acid to form amine 24. Aldehyde 25
reacts with amine 24 in the presence of MgSO₄ to form the intermediate imine, which is
reduced with sodium cyanoborohydride to afford compound 26.

Scheme 1
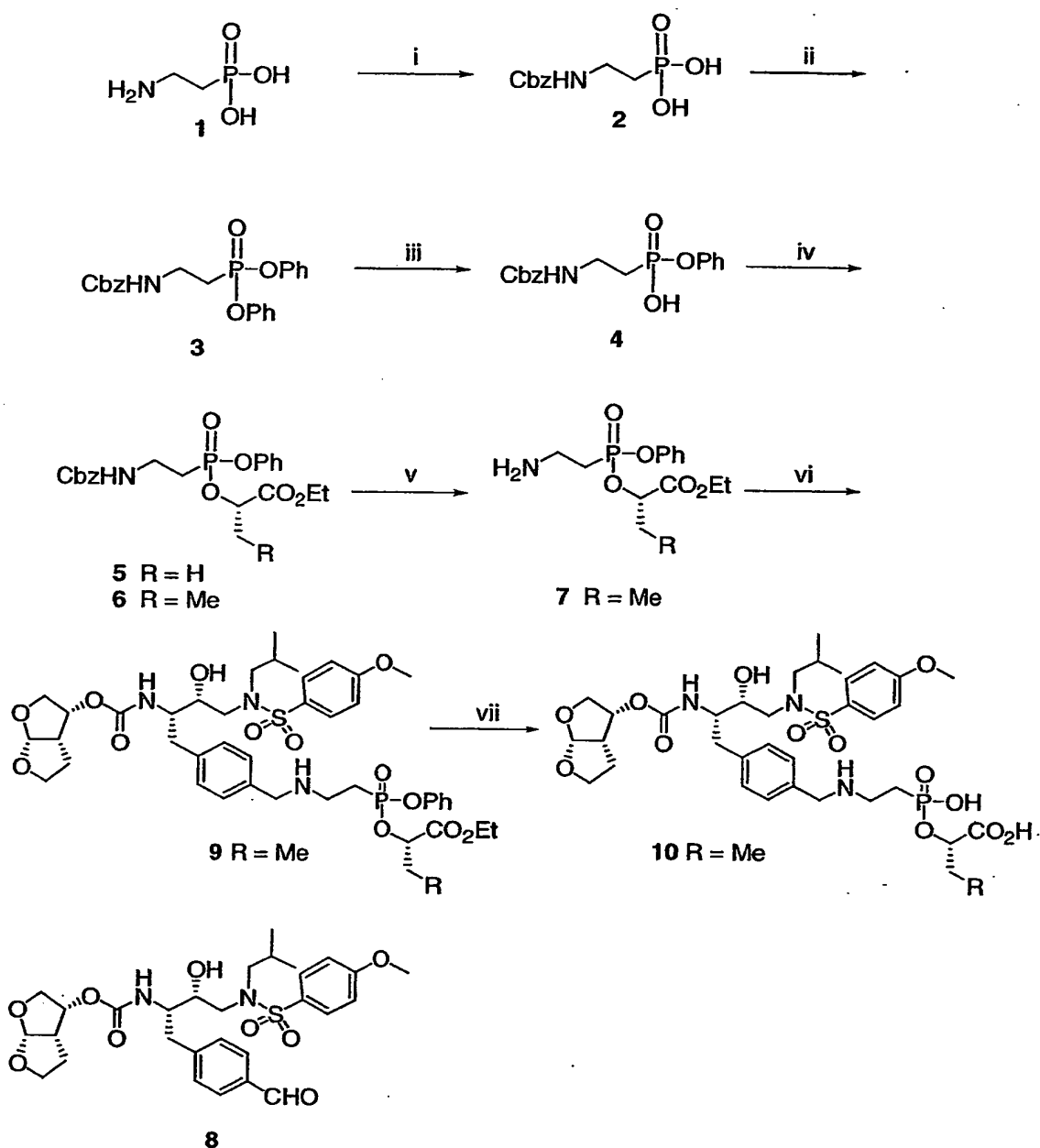
Reagents and conditions: i. CbzCl, NaOH, tol/H$_2$O, 100%; ii. a. SOCl$_2$, DMF, tol, 65°C; b. PhOH, Et$_3$N, CH$_2$Cl$_2$, 71%; iii. aq. NaOH, CH$_3$CN, 79%; iv. a. SOCl$_2$, DMF, tol, 65°C; b. ethyl lactate, Et$_3$N, CH$_2$Cl$_2$, (5) 85%; 2-hydroxy butyric acid ethyl ester, Et$_3$N, CH$_2$Cl$_2$, (6) 75%; v. H$_2$, AcOH, 10% Pd/C, EtOH, 94%; vi. a. 7 + 8, 1,2-DCE, MgSO$_4$; b. NaBH$_3$CN, AcOH, 50%; vii. pig liver esterase, 20% DMSO/PBS, 40°C, 25%.

Example 1

Compound 2: A 3L, 3-neck flask was equipped with a mechanical stirrer and addition funnel
and charged with 2-aminoethyl phosphonic acid (60.0g, 480 mmol). 2N Sodium hydroxide
5   (480 mL, 960 mmol) was added and flask cooled to 0°C. Benzyl chloroformate (102.4 g, 600
mmol) in toluene (160mL) was added dropwise with vigorous stirring. The reaction mixture
was stirred at 0°C for 30 minutes, then at room temperature for 4 h. 2N sodium hydroxide
(240 mL, 480 mmol) was added, followed by benzyl chloroformate (20.5 g, 120 mmol) and
the reaction mixture was vigorously stirred for 12 h. The reaction mixture was washed with
10   diethyl ether (3x). The aqueous layer was acidified to pH 2 with concentrated HCl to give a
white precipitate. Ethyl acetate was added to the mixture and concentrated HCl (80 mL, 960
mmol) was added. The aqueous layer was extracted with ethyl acetate and combined organic
layer was dried (MgSO$_4$) and concentrated to give a waxy, white solid (124 g, 479 mmol,
100%). ^{1}H NMR (300 MHz, CD$_3$OD): δ 7.45-7.30 (m, 5 H, Ar), 5.06 (d, J = 14.7 Hz, 2 H,
15   CH_2Ph), 3.44-3.31 (m, 2 H, NCH_2CH$_2$), 2.03-1.91 (m, 2 H, CH$_2$CH_2P); ^{31}P NMR (121 MHz,
CD$_3$OD): δ 26.3.

Example 2

Compound 3: To a mixture of compound 2 (50.0 g, 193 mmol) in toluene (1.0 L) was added
20   DMF (1.0 mL) followed by thionyl chloride (56 mL, 768 mmol). The reaction mixture was
heated at 65°C for 3-4 h under a stream of argon. The reaction mixture was cooled to room
temperature and concentrated. Residual solvent was removed under high vacuum for 1 h.
The residue was dissolved in CH$_2$Cl$_2$ (1.0 L) and cooled to 0°C. Triethylamine (161 mL,
1158 mmol) was added, followed by phenol (54.5 g, 579 mmol). The reaction mixture was
25   warmed to room temperature overnight, then washed with 1.0N HCl, saturated NaHCO$_3$
solution, brine and dried (MgSO$_4$). Concentrated and purified (silica gel, 1:1 EtOAc/Hex) to
give a pale yellow solid (56 g, 136 mmol, 71%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40-7.10
(m, 15 H, Ar), 5.53 (br s, 1 H, NH), 5.11 (br s, 2 H, CH_2Ph), 3.72-3.60 (m, 2 H, NCH_2CH$_2$),
2.49-2.30 (m, 2 H, CH$_2$CH_2P); ^{31}P NMR (121 MHz, CDCl$_3$): δ 22.9.

30

Example 3

Compound 4: To a solution of compound 3 (64 g, 155.6 mmol) in acetonitrile (500 mL) at 0°C was added 2.0M sodium hydroxide. The reaction mixture was stirred at 0°C for 30 min, then at room temperature for 2.5 h. The reaction mixture was concentrated to 100 mL and diluted with H$_2$O (500 mL). The aqueous solution was washed with EtOAc (3 x 300 mL).

5   The aqueous layer was acidified to pH 1 with concentrated HCl, producing a white precipitated. The mixture was extracted with EtOAc (4 x 300 mL) and combined organic layer was washed with brine and dried (MgSO$_4$). Concentration gave a solid, which was recrystallized from hot EtOAc (450 mL) to give a white solid (41.04 g, 122 mmol, 79%). ^{1}H NMR (300 MHz, CD$_3$OD): δ 7.45-7.10 (m, 10 H, Ar), 5.09 (s, 2 H, CH$_2$Ph), 3.53-3.30 (m, 2

10   H, NCH$_2$CH$_2$), 2.25-2.10 (m, 2 H, CH$_2$CH$_2$P); ^{31}P NMR (121 MHz, CD$_3$OD): δ 24.5.

Example 4

Compound 5: To a mixture of compound 4 (28 g, 83 mmol) in toluene (500 mL) was added DMF (1.0 mL), followed by thionyl chloride (36.4 mL, 499 mmol). The mixture was heated

15   at 65°C for 2 h providing a pale yellow solution. The reaction mixture was concentrated and dried for 45 min under high vacuum. The residue was dissolved in anhydrous CH$_2$Cl$_2$ (350 mL) and cooled to 0°C. Triethylamine (45.3 mL, 332 mmol) was added slowly, followed by the dropwise addition of ethyl lactate (18.8 mL, 166 mmol). The reaction mixture was stirred at 0°C for 30 min, then warmed to room temperature overnight. The reaction mixture was

20   diluted with CH$_2$Cl$_2$ and washed with 1 N HCl, saturated NaHCO$_3$ solution, brine and dried (MgSO$_4$). Concentration and purification (silica gel, 1:5 to 1:0 EtOAc/Hex) gave a pale yellow oil (30.7 g, 71 mmol, 85%) as a mixture of diastereomers which were separated by HPLC (Dynamax reverse phase C–18 column, 60% acetonitrile/H$_2$O). More polar diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40-7.10 (m, 10 H, Ar), 5.65 (s, 1 H, NH),

25   5.12 (s, 2 H, CH$_2$Ph), 5.10-5.00 (m, 1 H, OCHC) 4.17 (q, J = 6.9 Hz, 2 H, OCH$_2$CH$_3$), 3.62 (dt, J$_1$ = 20.4 Hz, J$_2$ = 6.0 Hz, 2 H, NCH$_2$CH$_2$), 2.25 (dt, J$_1$ = 18.0 Hz, J$_2$ = 6.0 Hz, 2 H, CH$_2$CH$_2$P), 1.60 (dd, J$_1$ = J$_2$= 6.9 Hz, 3 H, CHCH$_3$), 1.23 (t, J = 6.9 Hz, 3 H, OCH$_2$CH$_3$); ^{31}P NMR (121 MHz, CDCl$_3$): δ 26.2. Less polar diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40-7.10 (m, 10 H, Ar), 5.87 (s, 1 H, NH), 5.13 (s, 2 H, CH$_2$Ph), 5.10-5.00 (dq, J$_1$ = J$_2$ = 6.9

30   Hz, 1 H, OCHC) 4.22 (q, J = 7.2 Hz, 2 H, OCH$_2$CH$_3$), 3.68 (dt, J$_1$ = 21.6 Hz, J$_2$ = 6.9 Hz, 2 H, NCH$_2$CH$_2$), 2.40-2.20 (m, 2 H, CH$_2$CH$_2$P), 1.49 (dd, J$_1$ = 70.2 Hz, J$_2$ = 6.9 Hz, 3 H, CHCH$_3$), 1.28 (t, J = 6.9 Hz, 3 H, OCH$_2$CH$_3$); ^{31}P NMR (121 MHz, CDCl$_3$): δ 28.3.

Example 5

Compound 6: 2-Hydroxy-butyric acid ethyl ester was prepared as follows: To a solution of
L-2-aminobutyric acid (100g, 970 mmol) in 1.0 N H_2SO_4 (2 L) at 0°C was added $NaNO_2$ (111

5 g, 1610 mmol) in H_2O (400 mL) over 2 h. The reaction mixture was stirred at room
temperature for 18h. Reaction mixture was extracted with EtOAc (4x) and combined organic
layer was dried ($MgSO_4$) and concentrated to give a yellow solid (41.5 g). This solid was
dissolved in absolute ethanol (500 mL) and concentrated HCl (3.27 mL, 39.9 mmol) was
added. Reaction mixture was heated to 80°C. After 24 h, concentrated HCl (3 mL) was

10 added and reaction continued for 24 h. Reaction mixture was concentrated and product was
distilled to give a colorless oil (31 g, 235 mmol, 59%).

To a mixture of compound 4 (0.22 g, 0.63 mmol) in anhydrous acetonitrile (3.0 mL) was
added thionyl chloride (0.184 mL, 2.52 mmol). The mixture was heated at 65°C for 1.5 h
providing a pale yellow solution. The reaction mixture was concentrated and dried for 45

15 min under high vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (3.3 mL) and
cooled to 0°C. Triethylamine (0.26 mL, 1.89 mmol) was added slowly, followed by the
dropwise addition of 2-hydroxy-butyric acid ethyl ester (0.167 mL, 1.26 mmol). The reaction
mixture was stirred at 0°C for 5 min, then warmed to room temperature overnight. The
reaction mixture was concentrated, dissolved in EtOAc and washed with 1.0 N HCl, saturated

20 $NaHCO_3$ solution, brine and dried ($MgSO_4$). Concentration and purification (silica gel, 3:2
EtOAc/Hex) gave a pale yellow oil (0.21 g, 0.47 mmol, 75%). For major diastereomer, ^1H
NMR (300 MHz, $CDCl_3$): δ 7.35-7.10 (m, 10 H, Ar), 5.91 (s, 1 H, NH)), 5.12 (s, 2 H,
CH_2Ph), 4.94-4.83 (m, 1 H, OCHC), 4.27-4.12 (m, 2 H, OCH_2CH$_3$), 3.80-3.50 (m, 2 H,
NCH_2CH$_2$), 2.39-2.19 (m, 2 H, CH$_2$CH_2P), 1.82-1.71 (m, 2 H, CHCH_2CH$_3$), 1.30-1.195 (m, 3

25 H, OCH$_2$CH_3), 0.81 (t, J = 7.5 Hz, 3 H, CHCH$_2$CH_3); ^{31}P NMR (120 MHz, $CDCl_3$): δ 28.3.
For minor diastereomer, ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.10 (m, 10 H, Ar), 5.74 (s, 1 H,
NH)), 5.11 (s, 2 H, CH_2Ph), 4.98-4.94 (m, 1 H, OCHC), 4.27-4.12 (m, 2 H, OCH_2CH$_3$), 3.80-
3.50 (m, 2 H, NCH_2CH$_2$), 2.39-2.19 (m, 2 H, CH$_2$CH_2P), 1.98-1.82 (m, 2 H, CHCH_2CH$_3$),
1.30-1.195 (m, 3 H, OCH$_2$CH_3), 1.00 (t, J = 7.5 Hz, 3 H, CHCH$_2$CH_3); ^{31}P NMR (121 MHz,

30 $CDCl_3$): δ 26.2.

Example 6

Compound 7: A mixture of compound 6, (0.53 g, 1.18 mmol) acetic acid (0.135 mL, 2.36 mmol) and 10% palladium on activated carbon (0.08 g) in absolute ethanol (12 mL) was stirred under a hydrogen atmosphere (1 atm) for 3 h. Reaction mixture was filtered through Celite, concentrated, and resubjected to identical reaction conditions. After 2 h, Celite was added to the reaction mixture and mixture was stirred for 2 min, then filtered through a pad of Celite and concentrated. Dried under high vacuum to give the diasteromeric acetate salt as a oil (0.42 g, 1.11 mmol, 94%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40-7.10 (m, 5 H, Ar), 5.00-4.80 (m, 1 H, OCHC), 4.28-4.10 (m, 2 H, OCH$_2$CH$_2$), 3.32-3.14 (m, 2 H, NCH$_2$CH$_2$), 2.45-2.22 (m, 2 H, CH$_2$CH$_2$P), 1.97 (s, 3 H, Ac), 1.97-1.70 (m, 2 H, CHCH$_2$CH$_3$), 1.30-1.18 (m, 3 H, OCH$_2$CH$_3$), 1.00 (t, J = 7.5 Hz, 1 H, CHCH$_2$CH$_3$), 0.80 (t, J = 7.5 Hz, 2 H, CHCH$_2$CH$_3$); ^{31}P NMR (121 MHz, CDCl$_3$): δ 27.6 (major, 1.85), 26.0 (minor, 1.01).

Example 7

Compound 9: A solution of aldehyde 8 (0.596 g, 1.01 mmol) and compound 7 (0.42 g, 1.11 mmol) were stirred together in 1,2-dichloroethane (4.0 mL) in the presence of MgSO$_4$ for 3 h. Acetic acid (0.231 mL, 4.04 mmol) and sodium cyanoborohydride (0.127 g, 2.02 mmol) were added and reaction mixture was stirred for 50 min at room temperature. Reaction mixture was quenched with saturated NaHCO$_3$ solution, diluted with EtOAc, and vigorously stirred for 5 min. Brine was added and extracted with EtOAc (2x). Combined organic layer was dried (MgSO$_4$) concentrated and purified (silica gel, EtOAc, then 10% EtOH/EtOAc) to give a colorless foam. Acetonitrile (4 mL) and trifluoroacetic acid (0.06 mL) were added and concentrated to a volume of 1 mL. H$_2$O (10 mL) was added and lyophilized to give the TFA salt as a white powder (0.51 g, 0.508 mmol, 50%). ^{1}H NMR (300 MHz, CD$_3$CN): δ 7.79 (d, J = 8.4 Hz, 2 H, (SO$_2$C(CH)$_2$), 7.43-7.20 (m, 9 H, Ar), 7.10 (d, J = 8.4 Hz, 2 H, (CH)$_2$COCH$_3$), 5.85 (d, J = 8.4 Hz, 1 H, NH), 5.55 (d, J = 4.5 Hz, 1 H, OCHO), 5.00-4.75 (m, 2 H, CH$_2$CHOC(O), POCHC), 4.39-4.05 (m, 2 H, PhCH$_2$N, OCH$_2$CH$_3$), 3.89 (s, 3 H, OCH$_3$), 3.88-3.30 (m, 9H), 3.15-2.84 (m, 5 H), 2.65-2.42 (m, 3 H), 2.10-1.68 (m, 5 H), 1.65-1.15 (m, 5 H), 1.05-0.79 (m, 9 H); ^{31}P NMR (121 MHz, CD$_3$CN): δ 24.8 (major, 1.85), 23.1 (minor, 1.01).

Example 8

Compound 10: Compound 9 (0.041 g, 0.041 mmol) was dissolved in DMSO (1.9 mL) and to this solution was added phosphate buffered saline, pH 7.4 (10 mL) and pig liver esterase

(Sigma, 0.2 mL). Reaction mixture was stirred for 24 h at 40°C. After 24 h, additional ·
esterase (0.2 mL) was added and reaction was continued for 24 h. Reaction mixture was
concentrated, resuspended in methanol and filtered. Filtrate was concentrated and purified by
reverse phase chromatography to give a white powder after lyophilization (8 mg, 0.010

5   mmol, 25%). ^{1}H NMR (500 MHz, CD$_3$OD): δ 7.78 (d, J = 8.9 Hz, 2 H, (SO$_2$C(CH)$_2$), 7.43-
7.35 (m, 4 H, Ar), 7.11 (d, J = 8.9 Hz, 2 H, (CH)$_2$COCH$_3$), 5.62 (d, J = 5.2 Hz, 1 H, OCHO),
4.96-4.77 (m, 2 H, CH$_2$CHOC(O), POCHC), 4.21 (br s, 2 H, PhCH_2N), 3.97-3.70 (m, 6 H),
3.90 (s, 3 H, OCH_3), 3.50-3.30 (m, 3 H), 3.26-3.02 (m, 2 H), 2.94-2.58 (m, 4 H), 2.09-1.78
(m, 5 H), 1.63-1.52 (m, 2 H), 1.05-0.97 (m, 3 H); 0.94 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7

10   Hz, 3 H); ^{31}P NMR (121 MHz, CD$_3$OD): δ 20.8.

Scheme 2

-1511-

16   v   **17**   vi

18   **13**
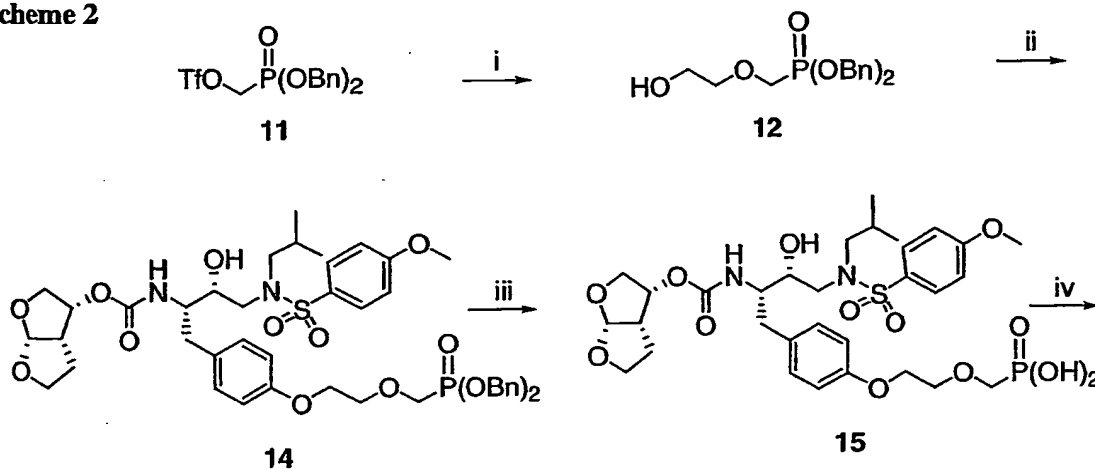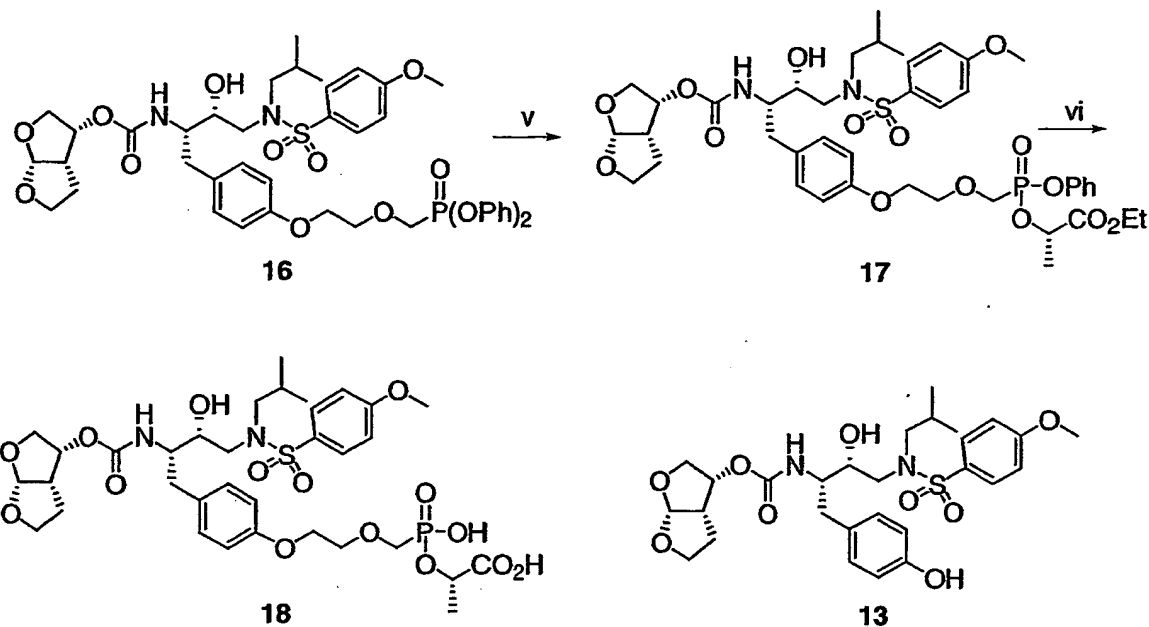
Reagents and conditions: i. ethylene glycol, Mg(OtBu)$_2$, DMF, 48%; ii. a. Tf$_2$O, 2,6-lutidine, CH$_2$Cl$_2$, -78°C; b. **13**, CsCO$_3$, CH$_3$CN, 0°C to room temperature, 65%; iii. H$_2$, Pd/C, EtOH, 107%; iv. DCC, PhOH, pyr, 70°C, 31%; v. a. NaOH, CH$_3$CN, 0°C; b. DCC, ethyl lactate, pyr, 70°C, 52%; vi. CH$_3$CN, DMSO, PBS, porcine liver esterase, 38°C, 69%.

Example 9

5   Compound 12: To a solution of compound **11** (4.10 g, 9.66 mmol) and anhydrous ethylene glycol (5.39 mL, 96.6 mmol) in anhydrous DMF (30 mL) at 0°C was added powdered magnesium *tert*-butoxide (2.05 g, 12.02 mmol). The reaction mixture was stirred at 0°C for 1.5 h, then concentrated. The residue was partitioned between EtOAc and H$_2$O and washed with 1 N HCl, saturated NaHCO$_3$ solution, and brine. Organic layer dried (MgSO$_4$),

10   concentrated and purified (silica gel, 4% MeOH/CH$_2$Cl$_2$) to give a colorless oil (1.55 g, 48%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.37 (s, 10 H, Ar), 5.40-5.05 (m, 4 H, CH_2Ph), 3.84 (d, J = 8.1 Hz, 2 H, PCH_2O), 3.70-3.60 (m, 4 H, OCH_2CH$_2$O, OCH$_2$CH_2O); ^{31}P NMR (121 MHz, CDCl$_3$): δ 22.7.

15 · Example 10

Compound 14: To a solution of compound **12** (0.75 g, 2.23 mmol) and 2,6-lutidine (0.78 mL, 6.69 mmol) in CH$_2$Cl$_2$ (20 mL) at −78°C was added trifluoromethanesulfonic anhydride (0.45

mL, 2.68 mmol). The reaction mixture was stirred at −78°C for 40 min, then diluted with CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$ and dried ($MgSO_4$). Concentration gave a yellow oil that was dissolved in anhydrous acetonitrile (20 mL). Phenol 13 (1.00 g, 1.73 mmol) was added to the solution, which was cooled to 0°C. Cesium carbonate (0.619 g,

5   1.90 mmol) was added and reaction mixture was stirred at 0°C for 2 h, then at room temperature for 1.5 h. Additional cesium carbonate (0.200 g, 0.61 mmol) was added and reaction was continued for 1.5 h, then filtered. Concentration of the filtrate and purification (silica gel, 3% MeOH/CH_2Cl_2) gave a yellow gum (1.005 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.34 (s, 10 H, PhCH_2O), 7.11 (d, J = 8.1Hz,

10   2 H, $CH_2C(CH)_2(CH)_2$), 6.98 (d, J = 8.7 Hz, 2 H, $(CH)_2COCH_3$), 6.78 (d, J = 8.7 Hz, 2 H, $(CH)_2COCH_2$), 5.62 (d, J = 5.4 Hz, 1 H, OCHO), 5.16-4.97 (m, 6 H), 4.05-3.65 (m, 12 H), 3.86 (s, 3 H, OCH_3), 3.19-2.66 (m, 7 H), 1.95-1.46 (m, 3 H), 0.92 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$), 0.88 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 21.9.

15   Example 11

Compound 15: A mixture of compound 14 (0.410 g, 0.457 mmol) and 10% palladium on carbon (0.066 g) in ethanol (5.0 mL) was stirred under a hydrogen atmosphere (1 atm) for 16 h. Celite was added and the mixture was stirred for 5 min, then filtered through Celite and concentrated to give a foam (0.350 g, 107%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.76 (d, J =

20   8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.15 (d, J = 8.4Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 7.08 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_3$), 6.82 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_2$), 5.59 (d, J = 5.4 Hz, 1 H, OCHO), 5.16-4.97 (masked by CD_3OH, 1 H), 4.09-4.02 (m, 2 H), 3.99-3.82 (m, 10 H), 3.88 (s, 3 H, OCH_3), 3.52-3.32 (m, 1 H), 3.21-2.75 (m, 5 H), 2.55-2.40 (m, 1 H), 2.10-1.95 (m, 1 H), 1.75-1.25 (m, 2 H), 0.93 (d, J = 6.3 Hz, 3 H, CH(CH_3)$_2$), 0.88 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$); ^{31}P

25   NMR (121 MHz, CD_3OD): δ 19.5.

Example 12

Compound 16: Compound 15 (0.350 g, 0.488 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL), each time filling with N_2. Residue was dissolved in anhydrous pyridine

30   (2.5 mL) and phenol (0.459 g, 4.88 mmol) was added. This solution was heated to 70°C, then 1,3-dicyclohexylcarbodiimide (0.403 g, 1.93 mmol) was added and reaction mixture was heated at 70°C for 7 h. Reaction mixture was concentrated, coevaporated with toluene and

residue obtained was diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 2% MeOH/CH$_2$Cl$_2$, then another column 75% EtOAc/Hex) to give a clear oil (0.1324 g, 31%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.71 (d, J = 8.7 Hz, 2 H, SO$_2$C(CH)$_2$), 7.41-7.18 (m, 10 H,

5   Ar), 7.14 (d, J = 8.4Hz, 2 H, CH$_2$C(CH)$_2$(CH)$_2$), 6.99 (d, J = 9.0 Hz, 2 H, (CH)$_2$COCH$_3$), 6.83 (d, J = 8.4 Hz, 2 H, (CH)$_2$COCH$_2$), 5.64 (d, J = 5.1 Hz, 1 H, OCHO), 5.16-4.92 (m, 2 H), 4.32-3.62 (m, 12 H), 3.87 (s, 3 H, OCH_3), 3.22-2.73 (m, 7 H), 1.95-1.75 (m, 3 H), 0.93 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$), 0.88 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$); ^{31}P NMR (121 MHz, CDCl$_3$): δ 14.3.

10

Example 13

Compound 17: To a solution of compound **16** (0.132 g, 0.152 mmol) in acetonitrile (1.5 mL) at 0°C was added 1.0 M NaOH (0.38 mL, 0.381 mmol). Reaction mixture was stirred for 2 h at 0°C, then Dowex 50 (H+) resin was added until pH = 1. The resin was removed by

15   filtration and the filtrate was concentrated and washed with EtOAc/Hex (1:2, 25 mL), then dried under high vacuum to give a clear film (0.103 g, 85%). This film was coevaporated with anhydrous pyridine (3 x 5 mL), filling with N$_2$. The residue was dissolved in anhydrous pyridine (1 mL) and ethyl lactate (0.15 mL, 1.30 mmol) was added and reaction mixture was heated at 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (0.107 g, 0.520 mmol) was added

20   and reaction mixture was stirred at 70°C for 2.5 h. Additional 1,3-dicyclohexylcarbodiimide (0.055 g, 0.270 mmol) was added and reaction continued for another 1.5 h. Reaction mixture was concentrated and coevaporated with toluene and diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 80 to 100% EtOAc/Hex) to give a white foam (0.0607 g, 52%). ^{1}H

25   NMR (300 MHz, CDCl$_3$): δ 7.71 (d, J = 8.7 Hz, 2 H, SO$_2$C(CH)$_2$), 7.39-7.16 (m, 5 H, Ar), 7.13 (d, J = 8.1Hz, 2 H, CH$_2$C(CH)$_2$(CH)$_2$), 6.99 (d, J = 9.0 Hz, 2 H, (CH)$_2$COCH$_3$), 6.82 (d, J = 8.4 Hz, 2 H, (CH)$_2$COCH$_2$), 5.64 (d, J = 5.1 Hz, 1 H, OCHO), 5.16-4.92 (m, 3 H), 4.35-3.65 (m, 14 H), 3.87 (s, 3 H, OCH_3), 3.22-2.73 (m, 7 H), 1.95-1.80 (m, 3 H), 1.59 (d, J = 6.9Hz, 1.5 H, CCHCH_3), 1.47 (d, J = 7.2 Hz, 1.5 H, CCHCH_3), 1.37-1.18 (m, 3 H), 0.92 (d, J

30   = 6.6 Hz, 3 H, CH(CH_3)$_2$), 0.88 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$); ^{31}P NMR (121 MHz, CDCl$_3$): δ 19.2, 17.2.

Example 14

Compound 18: Compound **17** (11.5 mg, 0.013 mmol) was dissolved in DMSO (0.14 mL)

and acetonitrile (0.29 mL). PBS (pH 7.4, 1.43 mL) was added slowly with stirring. Porcine

liver esterase (Sigma, 0.1 mL) was added and reaction mixture was gently stirred at 38°C.

5   After 24 h, additional porcine liver esterase (0.1 mL) and DMSO (0.14 mL) were added and

reaction mixture stirred for 48 h at 38°C. Reaction mixture concentrated and methanol was

added to precipitate the enzyme. The mixture was filtered, concentrated and purified by

reverse phase chromatography to give a white powder after lyophilization (7.1 mg, 69%). ^{1}H

NMR (300 MHz, CD$_3$OD): δ 7.76 (d, J = 8.7 Hz, 2 H, SO$_2$C(CH)$_2$), 7.15 (d, J = 8.4 Hz, 2 H,

10   CH$_2$C(CH)$_2$(CH)$_2$), 7.08 (d, J = 9.0 Hz, 2 H, (CH)$_2$COCH$_3$), 6.83 (d, J = 8.7 Hz, 2 H,

(CH)$_2$COCH$_2$), 5.59 (d, J = 5.1 Hz, 1 H, OCHO), 5.16-4.90 (masked by CD$_3$OH, 2 H), 4.19-

3.65 (m, 12 H), 3.88 (s, 3 H, OCH_3), 3.50-3.27 (m, 1 H), 3.20-2.78 (m, 5 H), 2.55-2.40 (m, 1

H), 2.05-1.90 (m, 1 H), 1.75-1.30 (m, 2 H), 1.53 (d, J = 6.6 Hz, 3 H, CCHCH_3), 0.93 (d, J =

6.6 Hz, 3 H, CH(CH_3)$_2$), 0.88 (d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$); ^{31}P NMR (121 MHz, CD$_3$OD):

15   δ 16.7.

Alternatively, compound **17** was prepared as described below (Scheme 3).

Scheme 3
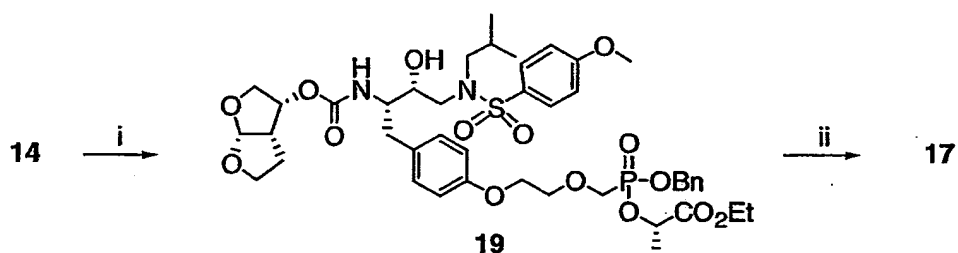
Reagents and conditions: i. a. **14**, DABCO, tol, reflux, b. ethyl lactate, PyBOP, DIPEA, DMF, 59%;
ii. a. H$_2$, Pd/C, EtOH; b. PhOH, PyBOP, DIPEA, DMF, 35%.

20

Example 15

Compound 19: To a solution of compound 14 (0.945 g, 1.05 mmol) in anhydrous toluene (10.0 mL) was added 1,4-diazobicyclo[2.2.2] octane (0.130 g, 1.16 mmol) and reaction mixture was refluxed for 2 h. After cooling to room temperature, reaction mixture was

5   diluted with EtOAc and washed with 1.0 N HCl and dried (MgSO$_4$). Concentration gave a white foam (0.785 g, 93%). Residue was dissolved in anhydrous DMF (10.0 mL) and to this solution was added ethyl (S)-lactate (0.23 mL, 2.00 mmol) and diisopropylethylamine (0.70 mL, 4.00 mmol), followed by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.041 g, 2.00 mmol). Reaction mixture was stirred for 20 h, then

10   concentrated and residue was dissolved in EtOAc and washed with 1.0 N HCl, saturated NaHCO$_3$, brine and dried (MgSO$_4$). Concentration and purification (silica gel, 2 % MeOH/CH$_2$Cl$_2$) gave an off-white foam (0.520 g, 59%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.72 (d, J = 7.5 Hz, 2 H, SO$_2$C(CH)$_2$), 7.50-7.27 (m, 4 H, Ar), 7.12 (d, J = 8.1Hz, 2 H, CH$_2$C(CH)$_2$(CH)$_2$), 7.00 (d, J = 6.6 Hz, 2 H, (CH)$_2$COCH$_3$), 6.81 (d, J = 8.4 Hz, 2 H,

15   (CH)$_2$COCH$_2$), 5.64 (d, J = 5.1 Hz, 1 H, OCHO), 5.37-4.90 (m, 5 H), 4.35-3.65 (m, 14 H), 3.88 (s, 3 H, OCH_3), 3.24-2.70 (m, 7 H), 1.90-1.70 (m, 3 H), 1.54 (d, J = 6.9Hz, 1.5 H, CCHCH_3), 1.47 (d, J = 6.9 Hz, 1.5 H, CCHCH_3), 1.37-1.22 (m, 3 H), 0.93 (d, J = 6.3 Hz, 3 H, CH(CH_3)$_2$), 0.89 (d, J = 6.0 Hz, 3 H, CH(CH_3)$_2$); ^{31}P NMR (121 MHz, CDCl$_3$): δ 22.3, 21.2.

20

Example 16

Compound 17: A mixture of compound 19 (0.520 g, 0.573 mmol) and 10% palladium on carbon (0.055 g) in ethanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then mixture was filtered

25   through Celite and concentrated to give a white foam (0.4649 g, 99%). Residue was dissolved in anhydrous DMF (5.0 mL) and to this solution was added phenol (0.097 g, 1.03 mmol), diisopropylethylamine (0.36 mL, 2.06 mmol) followed by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (0.536 g, 1.03 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and

30   washed with 1 N HCl, H$_2$O, sat. NaHCO$_3$, brine and dried (MgSO$_4$). Concentration and purification (silica gel, 2 % MeOH/CH$_2$Cl$_2$) gave a white foam (0.180 g, 35%).

Scheme 4
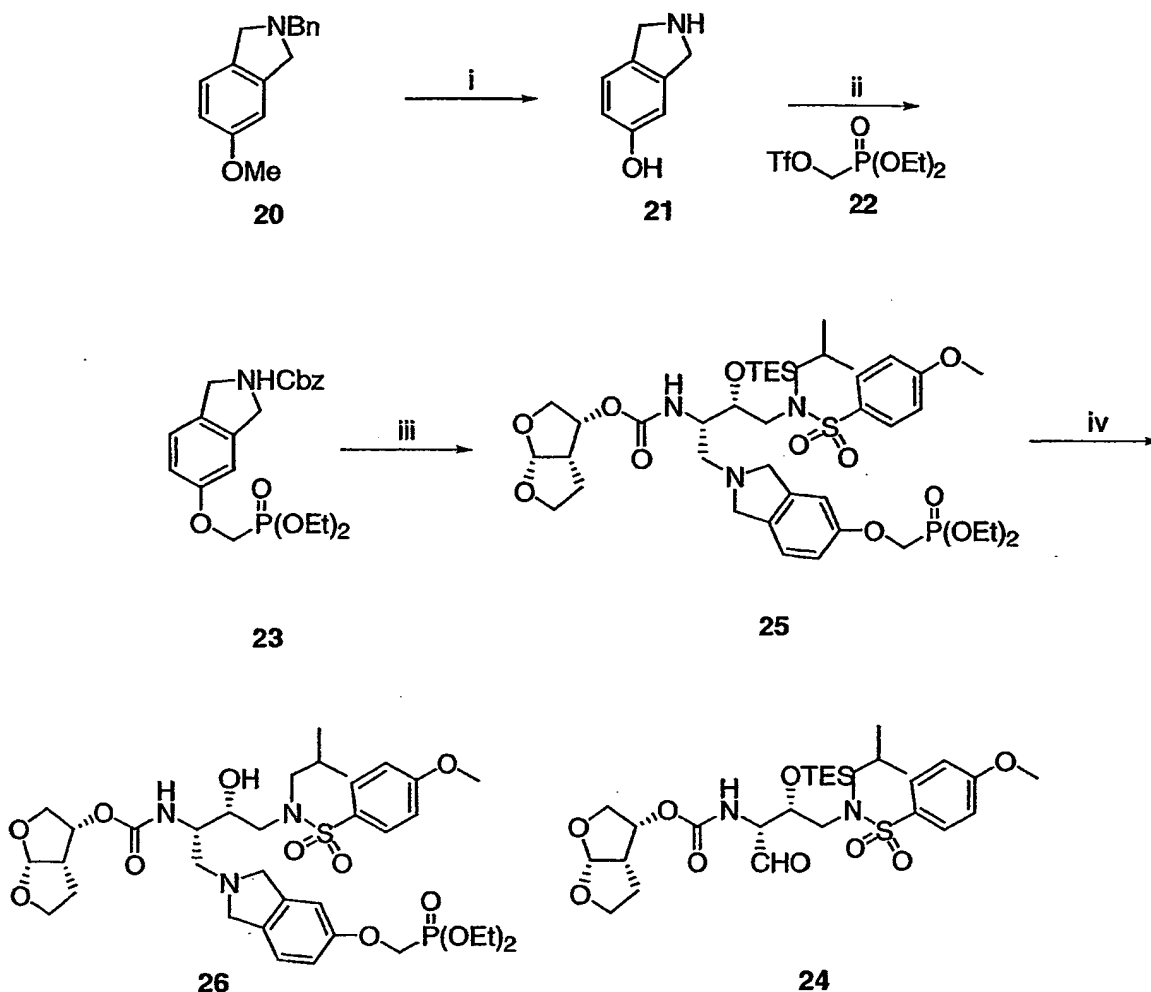
Reagents and conditions: i. a. 48% HBr, 120°C, 65%; b. H₂, Pd(OH)₂, EtOH, 100%;
ii. CbzCl, NaOH, tol/H₂O, 0°C to rt, 43%; b. **22**, CsCO₃, CH₃CN, 99%;
iii. a. H₂, Pd/C, AcOH, EtOAc/EtOH, 95%; b. **24**, NaBH(OAc)₃, 1,2-DCE, 21%;
iv, 4% HF/CH₃CN, 62%.

Example 17

5   Compound **21**: Compound **20** (11.5 g, 48.1 mmol) in 48% HBr (150 mL) was heated at

120°C for 4 h, then cooled to room temperature and diluted with EtOAc. Mixture was

neutralized with saturated NaHCO₃ solution and solid NaHCO₃ and extracted with EtOAc

containing MeOH. Organic layer dried (MgSO₄), concentrated, and purified (silica gel, 1:2

EtOAc/Hex with 1% MeOH) to give a brown solid (7.0 g, 65%). The resulting compound (7.0 g, 31.1 mmol) and 10% palladium hydroxide (2.1 g) in EtOH (310 mL) was stirred under a hydrogen atmosphere for 1 d, then filtered through Celite and concentrated to give an off-white solid (4.42 g, 100%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.01 (d, J = 7.8 Hz, 1 H, Ar),

5   6.64 (s, 1 H, Ar), 6.61 (d, J = 8.1 Hz, 2 H, Ar), 4.07 (s, 2 H, ArCH_2N), 4.05 (s, 2 H, ArCH_2N).

Example 18

Compound 22: To a solution of compound 21 (4.42 g, 32.7 mmol) in 1.0 M NaOH (98 mL,

10   98.25 mmol) at 0°C was added dropwise benzyl chloroformate (7.00 mL, 49.13 mmol) in toluene (7 mL). After addition was complete, reaction mixture was stirred overnight at room temperature. Reaction mixture was diluted with EtOAc and extracted with EtOAc (3x). Combined organic layer was dried (MgSO$_4$), concentrated and purified (silica gel, 2% MeOH/CH$_2$Cl$_2$) to give a white solid (3.786 g, 43%). The resulting compound (0.6546 g,

15   2.43 mmol) was dissolved in anhydrous acetonitrile (10 mL), and compound 23 (0.782 g, 2.92 mmol) was added, followed by cesium carbonate (1.583 g, 4.86 mmol). Reaction mixture was stirred for 2h at room temperature, then filtered, concentrated, and purified (3% MeOH/CH$_2$Cl$_2$) to give a brownish oil (1.01 g, 99%).

20   Example 19

Compound 25: To a solution of compound 22 (0.100 g, 0.238 mmol) in EtOAc/EtOH (2 mL, 1:1) was added acetic acid (14 μL, 0.238 mmol) and 10% palladium on carbon (0.020 g) and the mixture was stirred under a hydrogen atmosphere for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then filtered through Celite. Concentration and drying

25   under high vacuum gave a reddish film (0.0777 g, 95%). The resulting amine (0.0777g, 0.225 mmol) and aldehyde 24 (0.126 g, 0.205 mmol) in 1,2-dichloroethane (1.2 mL) were stirred for 5 min at 0°C, then sodium triacetoxyborohydride (0.0608 g, 0.287 mmol) was added. Reaction mixture was stirred for 1 h at 0°C, then quenched with saturated NaHCO$_3$ solution and brine. Extracted with EtOAc, the organic layer was dried (MgSO$_4$),

30   concentrated and purified (silica gel, 2% MeOH/CH$_2$Cl$_2$) to give a brown foam (38.7 mg, 21%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, J = 8.7 Hz, 2 H, Ar), 7.09 (d, J = 8.7 Hz, 1 H, Ar), 7.05-6.72 (m, 4 H, Ar), 5.71 (d, J = 5.1 Hz, 1 H), 5.22-5.07 (m, 2 H), 4.22-4.17 (m, 7 H),

4.16-3.69 (m, 9 H), 3.82 (s, 3 H), 3.25-2.51 (m, 7 H), 2.22-1.70 (m, 3 H), 1.37 (t, J = 6.9 Hz, 6 H), 1.10-0.58 (m, 21 H); ^{31}P NMR (121 MHz, CDCl$_3$): δ 19.5.

Example 20

5   Compound 26: To a solution of compound 25 (38.7 mg, 0.0438 mmol) in acetonitrile (0.5 mL) at 0°C was added 48% HF (0.02 mL). The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated NaHCO$_3$ solution and extracted with EtOAc. Organic layer was separated, dried (MgSO$_4$), concentrated and purified (silica gel, 3 to 5% MeOH/CH$_2$Cl$_2$) to give a red film (21.2 mg, 62%). ^{1}H NMR (300 MHz, CDCl$_3$): δ

10   7.73 (d, J = 8.7 Hz, 2 H, Ar), 7.10 (d, J = 8.7 Hz, 1 H, Ar), 6.97 (d, J = 8.70 Hz, 2 H), 6.90-6.76 (m, 2 H), 5.72 (d, J = 5.1 Hz, 1 H), 5.41 (d, J = 9.0 Hz, 1 H), 5.15 (q, J = 6.6 Hz, 1 H), 4.38-4.17 (m, 7 H), 4.16-3.65 (m, 9 H), 3.87 (s, 3 H), 3.20-2.82 (m, 7 H), 2.75-1.79 (m, 3 H), 1.37 (t, J = 6.9 Hz, 6 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{31}P NMR (121 MHz, CDCl$_3$): δ 19.3.

15

Scheme 5

-1519-
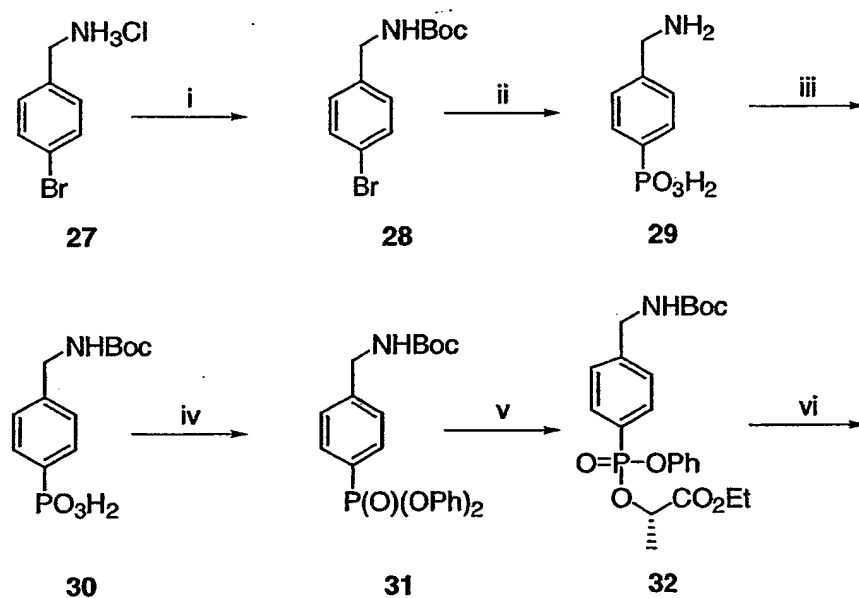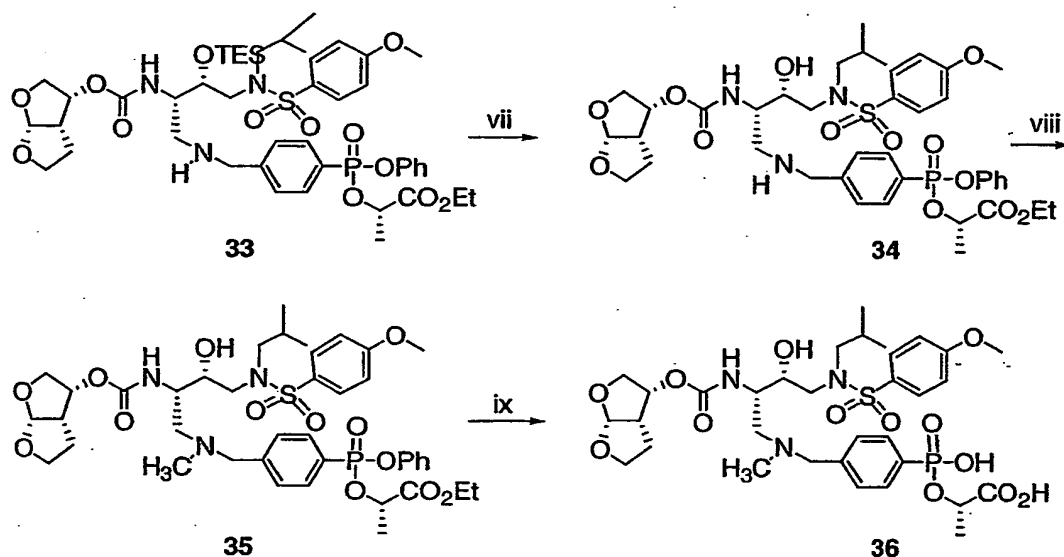
Reagents and conditions: i. Boc₂O, NaOH, H₂O, 96%;
ii. a. HP(OEt)₂, Et₃N, (PPh₃)₄Pd, 90°C, b. TMSBr, CH₃CN, 65%;
iii. Boc₂O, NaOH, THF/H₂O, 89%; iv. PhOH, DCC, pyr, 70°C, 71%;
v. a. NaOH, CH₃CN, 94%; b. Et lactate, DCC, pyr, 70°C, 80%; vi. a. TFA, CH₂Cl₂;
b. 24, AcOH, NaBH₃CN, EtOH, 33%; vii. 4% HF/CH₃CN, 88%;
viii. HCHO, AcOH, NaBH₃CN, EtOH, 67%;
ix. CH₃CN, DMSO, PBS, porcine liver esterase, 38°C, 21%.

Example 21

Compound 28: To a mixture of 4-bromobenzylamine hydrochloride (15.23 g, 68.4 mmol) in
H₂O (300 mL) was added sodium hydroxide (8.21 g, 205.2 mmol), followed by di-*tert*-butyl
dicarbonate (16.45g, 75.3 mmol). Reaction mixture was vigorously stirred for 18 h, then
diluted with EtOAc (500 mL). Organic layer separated and aqueous layer extracted with
EtOAc (200 mL). Combined organic layer was dried (MgSO₄), concentrated and dried under
high vacuum to give a white solid (18.7 g, 96%). ¹H NMR (300 MHz, CDCl₃): δ 7.41 (d, $J =$
8.4 Hz, 2 H), 7.12 (d, $J = 8.3$ Hz, 2 H), 4.82 (s, 1 H, NH), 4.22 (d, $J = 6.1$ Hz, 2 H), 1.41 (s, 9
H).

Example 22

Compound 29: Compound 28 (5.00 g, 17.47 mmol) was coevaporated with toluene. Diethyl
phosphite (11.3 mL, 87.36 mmol) was added and mixture was coevaporated with toluene

(2x). Triethylamine (24.0 mL, 174.7 mmol) was added and mixture was purged with argon

for 10 min, then tetrakis(triphenylphosphine) palladium(0) (4.00 g, 3.49 mmol) was added.

Reaction mixture was refluxed for 18 h, cooled, concentrated and diluted with EtOAc.

Washed with 0.5 N HCl, 0.5 M NaOH, H₂O, brine and dried (MgSO₄). Concentrated and

5   purification (silica gel, 70% EtOAc/Hex) gave an impure reaction product as a yellow oil (6.0

g). This material (6.0 g) was dissolved in anhydrous acetonitrile (30 mL) and cooled to 0°C.

Bromotrimethylsilane (11.5 mL, 87.4 mmol) was added and reaction mixture was warmed to

room temperature over 15 h. Reaction mixture was concentrated, dissolved in MeOH (50

mL) and stirred for 1.5 h. H₂O (1 mL) was added and mixture stirred for 2 h. Concentrated

10   to dryness and dried under high vacuum, then triturated with Et₂O containing 2% MeOH to

give a white solid (3.06 g, 65 %). ^{1}H NMR (300 MHz, D₂O): δ 7.67 (dd, J = 12.9, 7.6 Hz, 2

H), 7.45-7.35 (m, 2 H), 4.10 (s, 2 H); ^{31}P NMR (121 MHz, D₂O): δ 12.1.

Example 23

15   Compound 30: Compound **29** (4.78 g, 17.84 mmol) was dissolved in H₂O (95 mL)

containing sodium hydroxide (3.57 g, 89.20 mmol). Di-*tert*-butyl dicarbonate (7.63 g, 34.94

mmol) was added, followed by THF (25 mL). The clear reaction mixture was stirred

overnight at room temperature then concentrated to ~100 mL. Washed with EtOAc and

acidified to pH 1 with 1 N HCl and extracted with EtOAc (7x). Combined organic layer was

20   dried (MgSO₄), concentrated and dried under high vacuum. Trituration with Et₂O gave a

white powder (4.56 g, 89%). ^{1}H NMR (300 MHz, CD₃OD): δ 7.85-7.71 (m, 2 H), 7.39-7.30

(m, 2 H), 4.26 (s, 2 H), 1.46 (s, 9 H); ^{31}P NMR (121 MHz, CD₃OD): δ 16.3.

Example 24

25   Compound 31: Compound **30** (2.96 g, 10.32 mmol) was coevaporated with anhydrous

pyridine (3 x 10 mL). To this residue was added phenol (9.71 g, 103.2 mmol) and mixture

was coevaporated with anhydrous pyridine (2 x 10 mL). Pyridine (50 mL) was added and

solution heated to 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (8.51 g, 41.26 mmol)

was added and resulting mixture was stirred for 8 h at 70°C. Reaction mixture was cooled

30   and concentrated and coevaporated with toluene. Residue obtained was diluted with EtOAc

and the resulting precipitate was removed by filtration. The filtrate was concentrated and

purified (silica gel, 20 to 40% EtOAc/Hex, another column 30 to 40% EtOAc/Hex) to give a

white solid (3.20 g, 71%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.90 (dd, J = 13.8, 8.2 Hz, 2 H), 7.41-7.10 (m, 14 H), 5.17 (br s, 1 H, NH), 4.35 (d, J = 5.2 Hz, 2 H), 1.46 (s, 9 H); ^{31}P NMR (121 MHz, CDCl$_3$): δ 11.8.

5   Example 25

Compound 32: To a solution of compound 31 (3.73 g, 8.49 mmol) in acetonitrile (85 mL) at 0°C was added 1 M NaOH (21.2 mL, 21.21 mmol). Reaction mixture was stirred at 0°C for 30 min, then warmed to room temperature over 4 h. Reaction mixture cooled to 0°C and Dowex (H+) residue was added to pH 2. Mixture was filtered, concentrated and residue

10   obtained was triturated with EtOAc/Hex (1:2) to give a white powder (2.889 g, 94%). This compound (2.00 g, 5.50 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). The residue was dissolved in anhydrous pyridine (30 mL) and ethyl (S)-lactate (6.24 mL, 55 mmol) and reaction mixture was heated to 70°C. After 5 min, 1,3-dicyclocarbodiiimide (4.54 g, 22.0 mmol) was added. Reaction mixture was stirred at 70°C for 5 h, then cooled and

15   concentrated. Residue was dissolved in EtOAc and precipitate was removed by filtration. The filtrate was concentrated and purified (25 to 35% EtOAc/Hex, another column 40% EtOAc/Hex) to give a colorless oil (2.02 g, 80%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.96-7.85 (m, 2 H), 7.42-7.35 (m, 2 H), 7.35-7.08 (m, 4 H), 5.16-5.00 (m, 1 H), 4.93 (s, 1 H, NH), 4.37 (d, J = 5.5 Hz, 1 H), 4.21 (q, J = 7.3 Hz, 1 H), 4.11 (dq, J = 5.7, 2.2 Hz, 1 H), 1.62-1.47 (m, 3

20   H), 1.47 (s, 9 H), 1.27 (t, J = 7.3 Hz, 1.5 H), 1.17 (t, J = 7.3 Hz, 1.5 H); ^{31}P NMR (121 MHz, CDCl$_3$): δ 16.1, 15.0.

Example 26

Compound 33: Compound 32 (2.02 g, 4.36 mmol) was dissolved in CH$_2$Cl$_2$ (41 mL) and

25   cooled to 0°C. To this solution was added trifluoroacetic acid (3.5 mL) and reaction mixture was stirred at 0°C for 1 h, then at room temperature for 3 h. Reaction mixture was concentrated, coevaporated with EtOAc and diluted with H$_2$O (400 mL). Mixture was neutralized with Amberlite IRA-67 weakly basic resin, then filtered and concentrated. Coevaporation with MeOH and dried under high vacuum to give the TFA amine salt as a

30   semi-solid (1.48 g, 94%). To a solution of the amine (1.48 g, 4.07 mmol) in absolute ethanol (20 mL) at 0°C was added aldehyde 24 (1.39 g, 2.26 mmol), followed by acetic acid (0.14 mL, 2.49 mmol). After stirring for 5 min, sodium cyanoborohydride (0.284 g, 4.52 mmol)

was added and reaction mixture stirred for 30 min at 0°C. Reaction was quenched with saturated NaHCO₃ solution and diluted with EtOAc and H₂O. Aqueous layer was extracted with EtOAc (3x) and combined organic layer was dried (MgSO₄), concentrated and purified (silica gel, 2 to 4% MeOH/CH₂Cl₂) to give white foam (0.727 g, 33%). ^{1}H NMR (300 MHz, CDCl₃): δ 7.98-7.86 (m, 2 H), 7.71 (d, J = 8.6 Hz, 2 H), 7.49 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.72 (d, J = 5.1 Hz, 1 H), 5.28-5.00 (m, 2 H), 4.30-3.72 (m, 12 H), 3.42-3.58 (m, 1 H), 3.20-2.68 (m, 7 H), 2.25-1.42 (m, 6 H), 1.26 (t, J = 7.2 Hz, 1.5 H), 1.17 (t, J = 7.2 Hz, 1.5 H), 1.08-0.50 (m, 21 H); ^{31}P NMR (121 MHz, CDCl₃): δ 16.1, 15.1.

Example 27

Compound 34: To a solution of compound 33 (0.727 g, 0.756 mmol) in acetonitrile (7.6 mL) at 0°C was added 48% hydrofluoric acid (0.152 mL) and reaction mixture was stirred for 40 min at 0°C, then diluted with EtOAc and H₂O. Saturated NaHCO₃ was added and aqueous layer was extracted with EtOAc (2x). Combined organic layer was dried (MgSO₄), concentrated and purified (silica gel, 4 to 5% MeOH/CH₂Cl₂) to give a colorless foam (0.5655 g, 88%). ^{1}H NMR (300 MHz, CDCl₃): δ 7.95-7.82 (m, 2 H), 7.67 (d, J = 8.1 Hz, 2 H), 7.41 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.95 (d, J = 7.2 Hz, 2 H), 5.76 (d, J = 7.9 Hz, 1 H), 5.67 (d, J = 5.0 Hz, 1 H), 5.32-4.98 (m, 2 H), 4.25-3.75 (m, 13 H), 3.25-2.70 (m, 7 H), 2.15-1.76 (m, 3 H), 1.53-1.41 (m, 3 H), 1.25-1.08 (m, 3 H), 0.87 (d, J = 4.2 Hz, 6 H); ^{31}P NMR (121 MHz, CDCl₃): δ 16.1, 15.0.

Example 28

Compound 35: To a solution of compound 33 (0.560 g, 0.660 mmol) in absolute ethanol (13 mL) at 0°C was added 37% formaldehyde (0.54 mL, 6.60 mmol), followed by acetic acid (0.378 mL, 6.60 mmol). The reaction mixture was stirred at 0°C for 5 min, then sodium cyanoborohydride (0.415 g, 6.60 mmol) was added. Reaction mixture was warmed to room temperature over 2 h, then quenched with saturated NaHCO₃ solution. EtOAc was added and mixture was washed with brine. Aqueous layer was extracted with EtOAc (2x) and combined organic layer was dried (MgSO₄), concentrated and purified (silica gel, 3% MeOH/CH₂Cl₂) to give a white foam (0.384 g, 67%). ^{1}H NMR (300 MHz, CDCl₃): δ 7.95-7.82 (m, 2 H), 7.71 (d, J = 8.4 Hz, 2 H), 7.38 (br s, 2 H), 7.34-7.10 (m, 5 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.72 (d, J = 5.0 Hz, 1 H), 5.50 (br s, 1 H), 5.19-5.01 (m, 2 H), 4.29-3.75 (m, 10 H),

3.85 (s, 3 H), 3.35-2.70 (m, 7 H), 2.23 (s, 3 H), 2.17-1.79 (m, 3 H), 1.54 (d, J = 6.9 Hz, 1.5 H), 1.48 (d, J = 6.8 Hz, 1.5 H), 1.25 (t, J = 7.2 Hz, 1.5 H), 1.16 (t, J = 7.2 Hz, 1.5 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H). ^{31}P NMR (121 MHz, CDCl$_3$): δ 16.0, 14.8.

5   Example 29

Compound 36: To a solution of compound 35 (44 mg, 0.045 mmol) in acetonitrile (1.0 mL) and DMSO (0.5 mL) was added phosphate buffered saline (pH 7.4, 5.0 mL) to give a cloudy white suspension. Porcine liver esterase (200 μL) was added and reaction mixture was stirred for 48 h at 38°C. Additional esterase (600 μL) was added and reaction was continued for 4 d.

10   Reaction mixture was concentrated, diluted with MeOH and the resulting precipitate removed by filtration. Filtrate was concentrated and purified by reverse phase HPLC to give a white powder after lyophilization (7.2 mg, 21%). ^{1}H NMR (300 MHz, CD$_3$OD): δ 7.95 (br s, 2 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.64 (br s, 2 H), 7.13 (d, J = 8.7 Hz, 2 H), 5.68 (d, J = 5.1 Hz, 1 H), 5.14 (br s, 1 H), 4.77 (br s, 1 H), 4.35-3.59 (m, 8 H), 3.89 (s, 3 H), 3.45-2.62 (m, 10 H), 2.36-

15   1.86 (m, 3 H), 1.44 (d, J = 6.3 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{31}P NMR (121 MHz, CD$_3$OD): δ 13.8.

Scheme 1

GS 192771

GS 192772

Scheme 2

GS 191484

GS 192781

Scheme 3

(1) TFA, CH$_2$Cl$_2$

(2) TEA, —N⟨ ⟩N-SO$_2$Cl

Pd / C, H$_2$, r.t.
EtOAc, 2-propanol

Scheme 4

(1) Dibenzyldiisopropyl-
    phosphoramidite
    1H-tetrazole, r.t.

(2) Iodobenzenediacetate

(1) Pd / C, H$_2$
    EtOH / EtOAc

(2) NaHCO$_3$, H$_2$O

Scheme 5

(1) Dibenzyldiisopropyl-
   phosphoramidite
   1H-tetrazole, r.t.
(2) Iodobenzenediacetate

(1) Pd / C, H$_2$
   EtOH / EtOAc
(2) NaHCO$_3$, H$_2$O
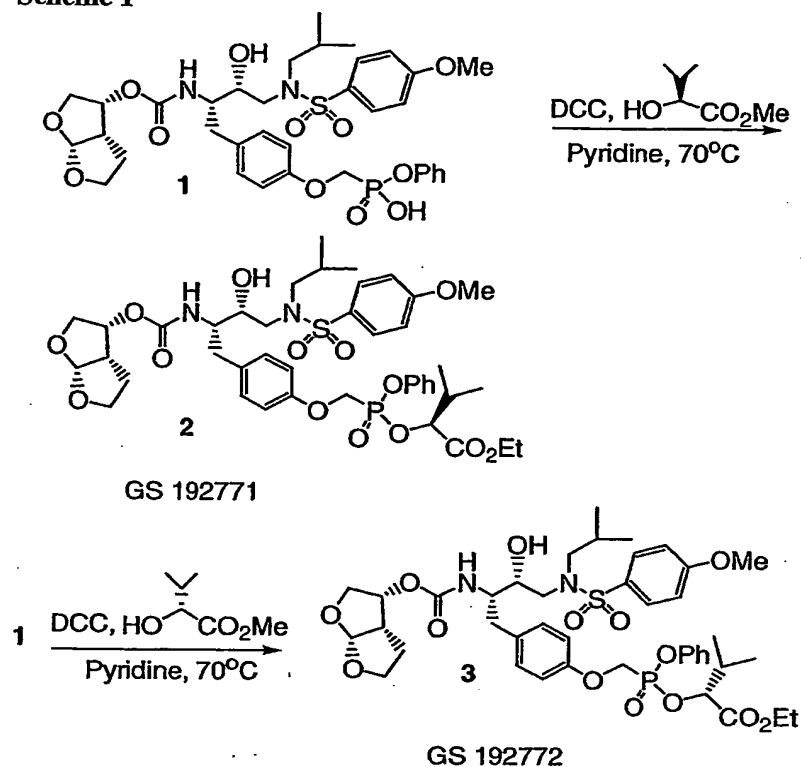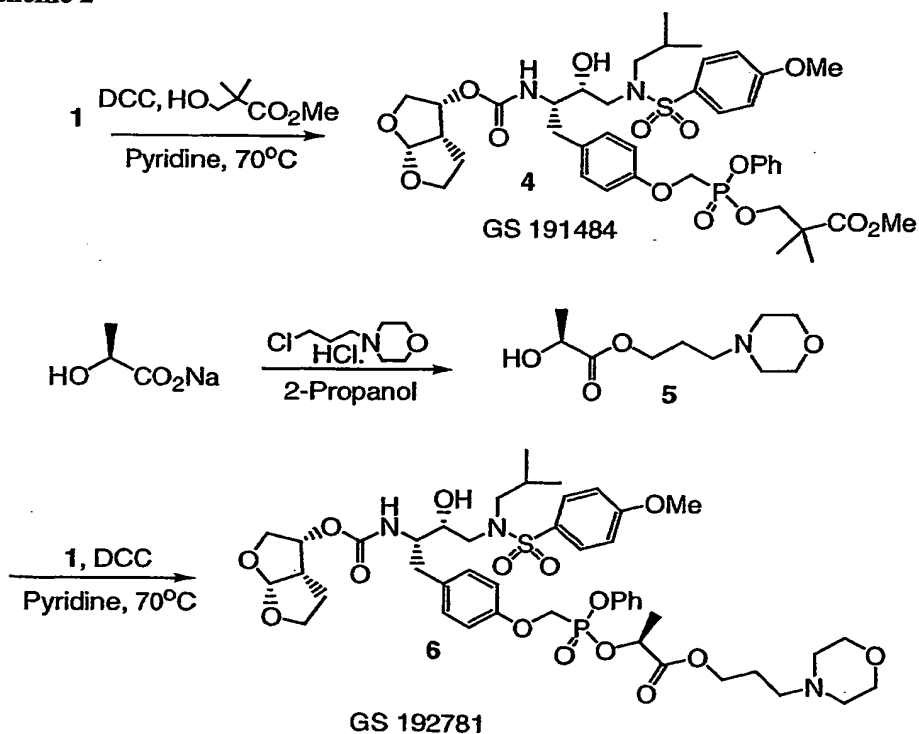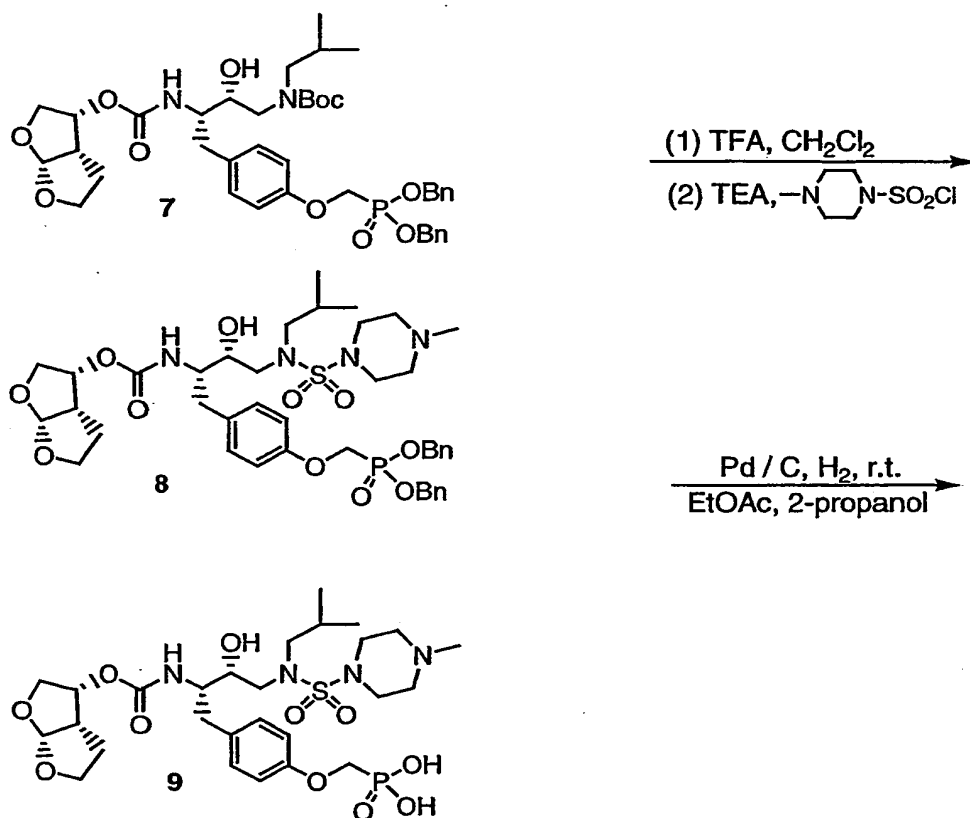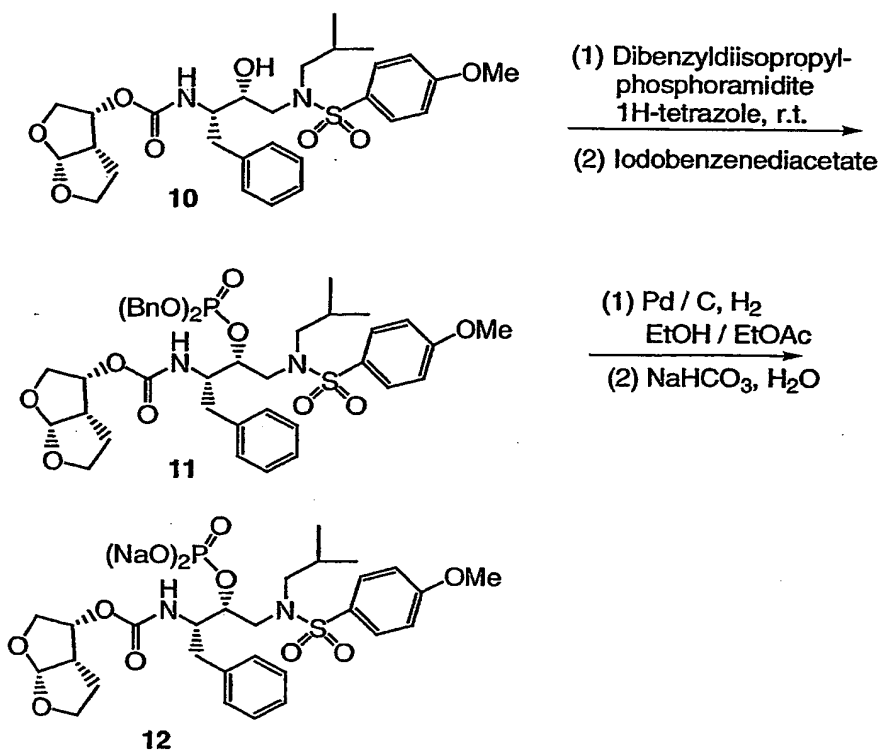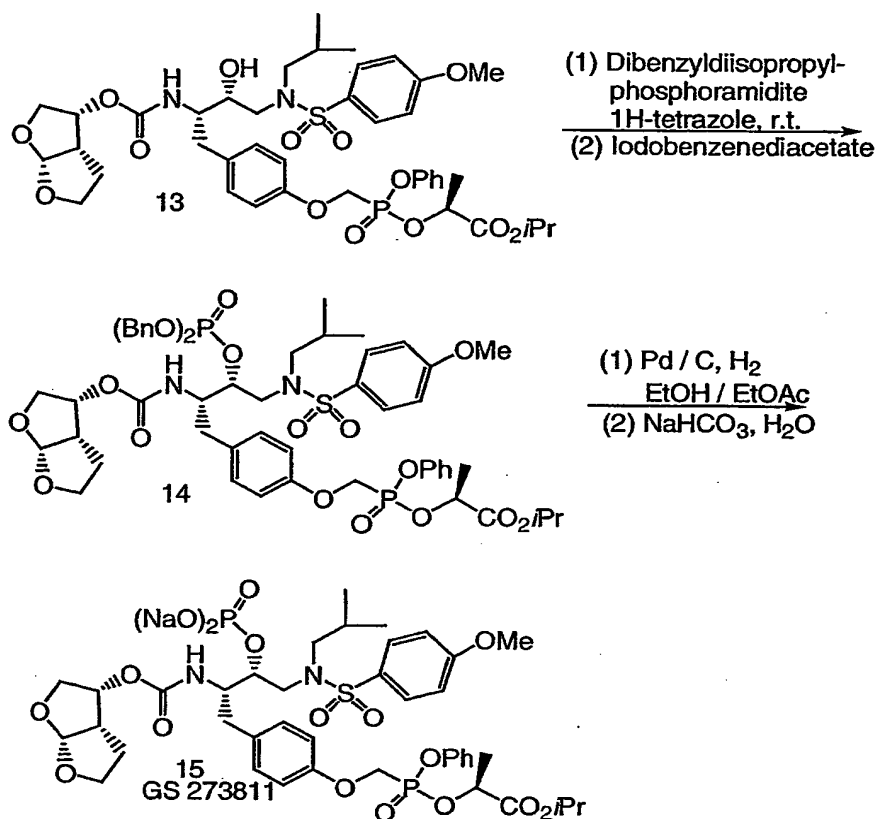
5   <u>Example 1</u>

Monophospholactate 2: A solution of 1 (0.11 g, 0.15 mmol) and α-hydroxyisovaleric acid
ethyl-(S)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-
dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred
at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced

10   pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off.
The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed
with 0.2 N HCl, H$_2$O, saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The
crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$)
to give the monophospholactate (35 mg, 28%, GS 192771, 1/1 diastereomeric mixture) as a

15   white solid: ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.36-7.14 (m, 7H), 6.99 (d, J = 8.7
Hz, 2H), 6.94-6.84 (dd, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.00-4.85 (m, 3H), 4.55 (dd, 1H), 4.41
(dd, 1H), 4.22-4.07 (m, 2H), 3.96-3.68 (m, 9H), 3.12-2.74 (m, 7H), 2.29 (m, 1H), 1.85-1.57

(m, 3H), 1.24 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.9 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.7, 15.1.

Example 2

5   Monophospholactate 3: A solution of 1 (0.11 g, 0.15 mmol) and α-hydroxyisovaleric acid ethyl-(R)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off.

10   The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H$_2$O, saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (35 mg, 28%, GS 192772, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.35-7.13 (m, 7H), 6.98 (d, J = 8.7

15   Hz, 2H), 6.93-6.83 (dd, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.04-4.85 (m, 3H), 4.54 (dd, 1H), 4.39 (dd, 1H), 4.21-4.06 (m, 2H), 3.97-3.67 (m, 9H), 3.12-2.75 (m, 7H), 2.27 (m, 1H), 1.83-1.57 (m, 3H), 1.26 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.9 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.7, 15.1.

20   Example 3

Monophospholactate 4: A solution of 1 (0.10 g, 0.13 mmol) and methyl-2,2-dimethyl-3-hydroxypropionate (56 μL, 0.44 mmol) in pyridine (1 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (91 mg, 0.44 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced

25   pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H$_2$O, saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (72 mg, 62%, GS 191484) as a white solid: ^{1}H NMR

30   (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.34 (m, 2H), 7.25-7.14 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.05 (m, 2H), 4.38 (d, J = 9.6 Hz, 2H),

4.32-4.20 (m, 2H), 4.00 (m, 2H), 3.87-3.63 (m, 12H), 3.12-2.78 (m, 7H), 1.85-1.67 (m, 3H), 1.20 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 16.0.

Example 4

5   Lactate 5: To a suspension of lactic acid sodium salt (5 g, 44.6 mmol) in 2-propanol (60 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (8.30 g, 44.6 mmol). The reaction mixture was heated to reflux for 18 h and cooled to room temperature. The solid was filtered and the filtrate was recrystallized from EtOAc / hexane to give the lactate (1.2 g, 12%).

10   Example 5

Monophospholactate 6: A solution of 1 (0.10 g, 0.13 mmol) and lactate 5 (0.10 g, 0.48 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended

15   in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and H$_2$O. The EtOAc layer was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (30 mg, 24%, GS 192781, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H),

20   7.38-7.15 (m, 7H), 7.00 (d, J = 8.7 Hz, 2H), 6.91 (m, 2H), 5.65 (d, J = 3.3 Hz, 1H), 5.18-4.98 (m, 3H), 4.54 (dd, 1H), 4.42 (dd, 1H), 4.2 (m, 2H), 4.00-3.67 (m, 16H), 3.13-2.77 (m, 7H), 2.4 (m, 5H), 1.85-1.5 (m, 5H), 1.25 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4, 15.4.

25   Example 6

Sulfonamide 8: A solution of dibenzylphosphonate 7 (0.1 g, 0.13 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-

30   evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (1 mL) and cooled to 0°C. Triethylamine (72 μL, 0.52 mmol) was added followed by the treatment of 4-methylpiperazinylsulfonyl chloride (25 mg, 0.13 mmol). The solution was stirred for 1 h at

0°C and the product was partitioned between CH_2Cl_2 and H_2O. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the sulfonamide 8 (32 mg, 30%, GS 273835) as a white solid:

5   ^{1}HNMR (CDCl$_3$) δ 7.35 (m, 10H), 7.11 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.91 (m, 4H), 4.2 (d, J = 10.2 Hz, 2H), 4.0-3.69 (m, 6H), 3.4-3.19 (m, 5H), 3.07-2.75 (m, 5H), 2.45 (m, 4H), 2.3 (s, 3H), 1.89-1.44 (m, 7H), 0.93 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 20.3.

10   Example 7

Phosphonic Acid 9: To a solution of 8 (20 mg, 0.02 mmol) in EtOAc (2 mL) and 2-propanol (0.2 mL) was added 10% Pd/C (5 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (10

15   mg, 64%) as a white solid.

Example 8

Dibenzylphosphonate 11: A solution of 10 (85 mg, 0.15 mmol) and 1H-tetrazole (14 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was treated with Dibenzyldiisopropylphosphoramidite (60 μL,

20   0.20 mmol) and stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (85 mg, 0.11 mmol) which was dissolved in CH_3CN (2 mL) and treated with iodobenzenediacetate (51 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated.

25   The residue was partitioned between EtOAc and NaHCO$_3$. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (45 mg, 52%) as a white solid.

30   Example 9

Disodium Salt of Phosphonic Acid 12: To a solution of 11 (25 mg, 0.03 mmol) in EtOAc (2 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of

-1531-

celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid which was dissolved in H_2O (1mL) and treated with $NaHCO_3$ (2.53 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (19.77 mg, 95%, GS 273777) as a white solid: ^{1}H NMR
5   (CD_3OD) δ 7.81 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.27-7.09 (m, 5H), 5.57 (d, J = 5.1 Hz, 1H), 5.07 (m, 1H), 4.87-4.40 (m, 3H), 3.93-3.62 (m, 6H), 3.45-2.6 (m, 6H), 2.0 (m, 2H), 1.55 (m, 1H), 0.95-0.84 (m, 6H).

Example 10

10   Dibenzylphosphonate 14: A solution of 13 (0.80 g, 0.93 mmol) and 1H-tetrazole (98 mg, 1.39 mmol) in CH_2Cl_2 (15 mL) was treated with dibenzyldiisopropylphosphoramidite (0.43 mL, 1.39 mmol) and stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (0.68 g,
15   67%). To a solution of the dibenzylphosphite (0.39 g, 0.35 mmol) in CH_3CN (5 mL) was added iodobenzenediacetate (0.17 g, 0.53 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was partitioned between EtOAc and $NaHCO_3$. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3%
20   2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (0.35 g, 88%) as a white solid.

Example 11

Disodium Salt of Phosphonic Acid 15: To a solution of 14 (0.39 g, 0.35 mmol) in EtOAc (30 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H_2 atmosphere
25   (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid, which was dissolved in H_2O (3 mL) and treated with $NaHCO_3$ (58 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (0.31 g, 90%, GS 273811) as a white solid: ^{1}H NMR
30   (CD_3OD) δ 7.81 (d, J = 9.0 Hz, 2H), 7.43-7.2 (m, 7H), 7.13 (d, J = 9.0 Hz, 2H), 6.9 (m, 2H), 5.55 (d, J = 4.8 Hz, 1H), 5.07 (m, 2H), 4.87(m, 1H), 4.64-4.4 (m, 4H), 3.93-3.62 (m, 9H), 3.33-2.63 (m, 5H), 2.11 (m, 1H), 1.6-1.42 (m, 4H), 1.38-1.25 (m, 7H), 0.95 (d, J = 6.3 Hz, 3H), 0.84 (d, J = 6.3 Hz, 3H).

Examples For The Preparation Of Cyclic Carbonyl-Like Phosphonate Protease Inhibitors (CCPPI)

Phosphonamidate Prodrugs

5
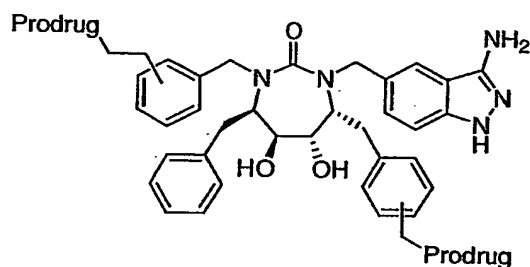
Scheme 1-2	Scaffold Synthesis
10 Scheme 3-10	P2'-Benzyl ether phosphonates
Scheme 11-13	P2'-Alkyl ether phosphonates
Scheme 14-17	P2'-Benzyl Amide phosphonates
Scheme 18-25	P1-Phosphonates
Scheme 50	Reagents

15

Scheme 1

1   1.1
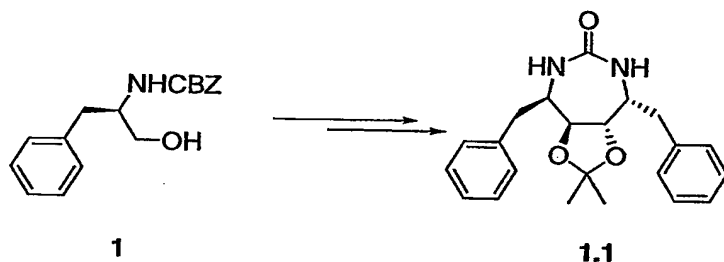
The conversion of **1** to **1.1** is described in J. Org Chem 1996, 61, p444-450

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Scheme 2
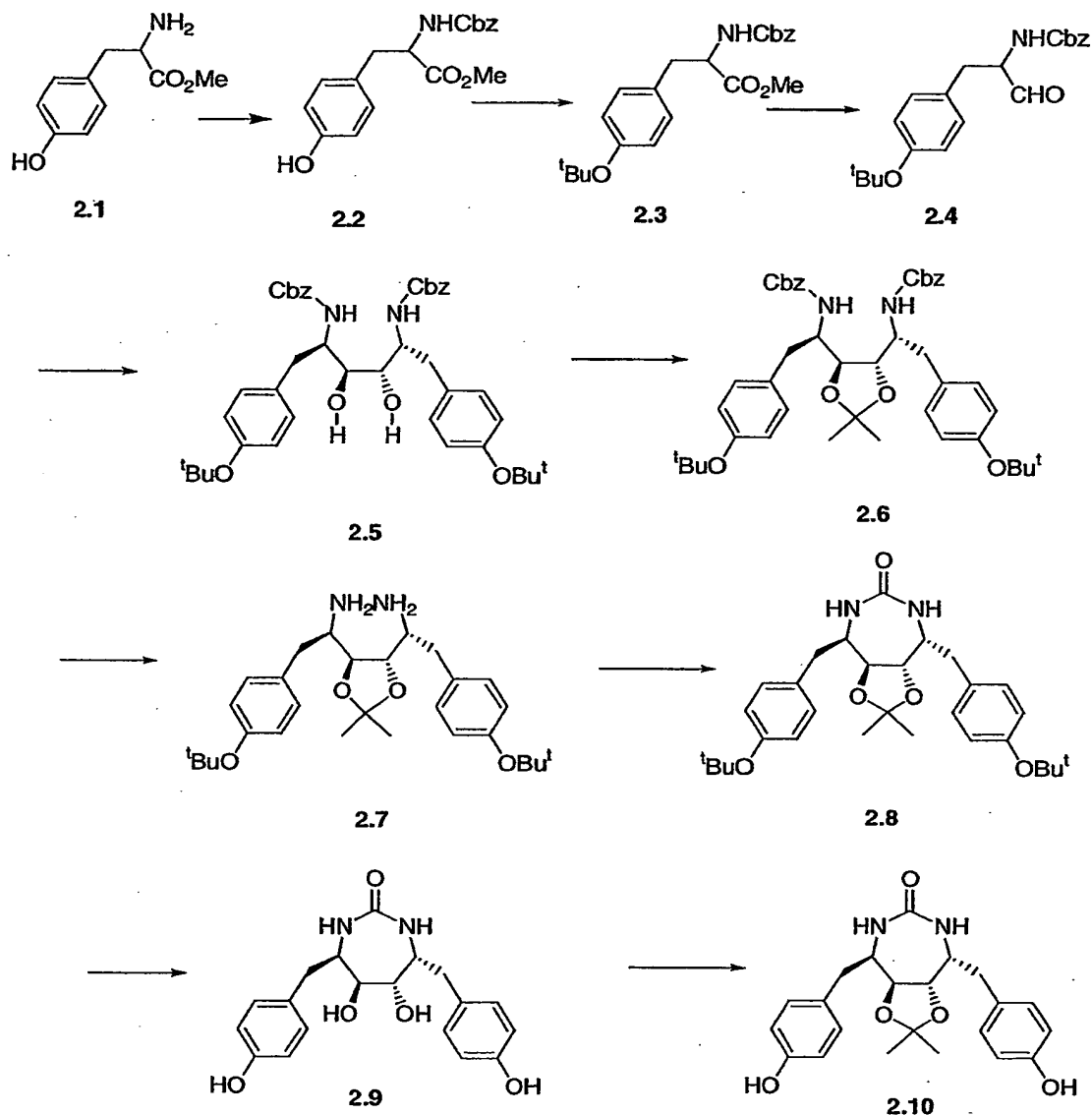
2-Benzyloxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid methyl ester (2.3)

H-D-Tyr-O-me hydrochloride **2.1** (25 g, 107.7 mmol) is dissolved in methylene chloride (150 mL) and aqueous sodium bicarbonate (22 g in 150 mL water), and then cooled to 0°C. To this resulting solution benzyl chloroformate (20 g, 118 mmol) is slowly added. After complete addition, the resulting solution is warmed to room temperature ,and is then stirred for 2 h. The organic phase is separated, dried over Na₂SO₄, and concentrated under reduced pressure, to give the crude carbamate **2.2** (35g). The crude CBZ-Tyr-OMe product is

dissolved in methylene chloride (300 mL) containing concentrated H₂SO₄. Isobutene is bubbled though the solution for 6 h. The reaction is then cooled to 0°C, and neutralized with saturated NaHCO₃ aqueous solution. The organic phase is separated, dried, concentrated under reduced pressure, and purified by silica gel column chromatography to afford the tert-

5   butyl ether 2.3 (25.7 g, 62 %).

[2-(4-tert-Butoxy-phenyl)-1-formyl-ethyl]-carbamic acid benzyl ester (2.4)
(Reference J. O. C. 1997, 62, 3884).

To a stirred –78°C methylene chloride solution (60 mL) of 2.3, DIBAL (82 mL of 1.5 M in

10   toluene, 123 mmol) was added over 15 min. The resultant solution was stirred at –78°C for 30 min. Subsequently, a solution of EtOH/36 % HCl (9/1; 15 mL) is added slowly. The solution is added to a vigorously stirred aqueous HCl solution (600 mL, 1N) at 0°C. The layers are then separated, and the aqueous phase is extracted with cold methylene chloride. The combined organic phases are washed with cold 1N HCl aqueous solution, water, dried

15   over Na₂SO₄, and then concentrated under reduced pressure to give the crude aldehyde 2.4 (20 g, 91 %).

[4-Benzyloxycarbonylamino-1-(4-tert-butoxy-benzyl)-5-(4-tert-butoxy-phenyl)-2,3-
dihydroxy-pentyl]-carbamic acid benzyl ester (2.5)

20   To a slurry of VCl₃(THF)₃ in methylene chloride (150 mL) at room temperature is added Zinc powder (2.9 g, 44 mmol), and the resulting solution is then stirred at room temperature for 1 hour. A solution of aldehyde 2.4 (20 g, 56 mmol) in methylene chloride (100 mL) is then added over 10 min. The resulting solution is then stirred at room temperature overnight, poured into an ice-cold H₂SO₄ aqueous solution (8 mL in 200 mL), and stirred at 0°C for 30

25   min. The methylene chloride solution is separated, washed with 1N HCl until the washing solution is light blue. The organic solution is then concentrated under reduced pressure (solids are formed during concentration), and diluted with hexane. The precipitate is collected and washed thoroughly with a hexane/methylene chloride mixture to give the diol product 2.5. The filtrate is concentrated under reduced pressure and subjected to silica gel

30   chomatography to afford a further 1.5 g of 2.5. (Total = 13 g, 65 %).

[1-{5-[1-Benzyloxycarbonylamino-2-(4-tert-butoxy-phenyl)-ethyl]-2,2-dimethyl-
[1,3]dioxolan-4-yl}-2-(4-tert-butoxy-phenyl)-ethyl]-carbamic acid benzyl ester (2.6)

Diol 2.5 (5 g, 7 mmol) is dissolved in acetone (120 mL), 2,2-dimethoxypropane (20 mL), and

pyridinium p-toluenesulfonate (120 mg, 0.5 mmol). The resulting solution is refluxed for 30

min., and then concentrated under reduced pressure to almost dryness. The resulting mixture

is partitioned between methylene chloride and saturated NaHCO$_3$ aqueous solution, dried,

5   concentrated under reduced pressure, and purified by silica gel column chomatography to

afford isopropylidene protected diol 2.6 (4.8 g, 92 %).

4,8-Bis-(4-tert-butoxy-benzyl)-2,2-dimethyl-hexahydro-1,3-dioxa-5,7-diaza-azulen-6-one(2.8)

10   The diol 2.6 is dissolved in EtOAc/EtOH (10 mL/2 mL) in the presence of 10 % Pd/C and

hydrogenated at atmospheric pressure to afford the diamino compound 2.7. To a solution of

crude 2.7 in 1,1,2,2-tetrachloroethane is added 1,1-carboxydiimidazole (1.05 g, 6.5 mmol) at

room temperature. The mixture is stirred for 10 min, and the resulting solution is then added

dropwise to a refluxing 1,1',2,2'-tetrachloroethane solution (150 mL). After 30 min., the

15   reaction mixture is cooled to room temperature, and washed with 5 % citric acid aqueous

solution, dried over Na$_2$SO4, concentrated under reduced pressure, and purified by silica gel

column chomatography to afford the cyclourea derivative 2.8 (1.92 g, 60 % over 2 steps).

20   **5,6-Dihydroxy-4,7-bis-(4-hydroxy-benzyl)-[1,3]diazepan-2-one (2.9)**

Cyclic Urea 2.8 (0.4 g, 0.78 mmol) was dissolved in dichloromethane (3 mL) and treated

with TFA (1 mL). The mixture was stirred at room temperature for 2 h upon which time a

white solid precipitated. 2 drops of water and methanol (2 mL) were added and the

homogeneous solution was stirred for 1 h and concentrated under reduced pressure. The

25   crude solid, 2.9, was dried overnight and then used without further purification.

4,8-Bis-(4-hydroxy-benzyl)-2,2-dimethyl-hexahydro-1,3-dioxa-5,7-diaza-azulen-6-one (2.10)

Diol 2.9 (1.8 g, 5.03 mmol) was dissolved in DMF (6 mL) and 2,2-dimethoxypropane (12

30   mL). P-TsOH (95 mg) was added and the mixture stirred at 65°C for 3 h. A vacuum was

applied to remove water and then the mixture was stirred at 65°C for a further 1 h. The

excess dimethoxypropane was then distilled and the remaining DMF solution was then

allowed to cool. The solution of acetonide **2.10** can then used without further purification in future reactions.

Scheme 3
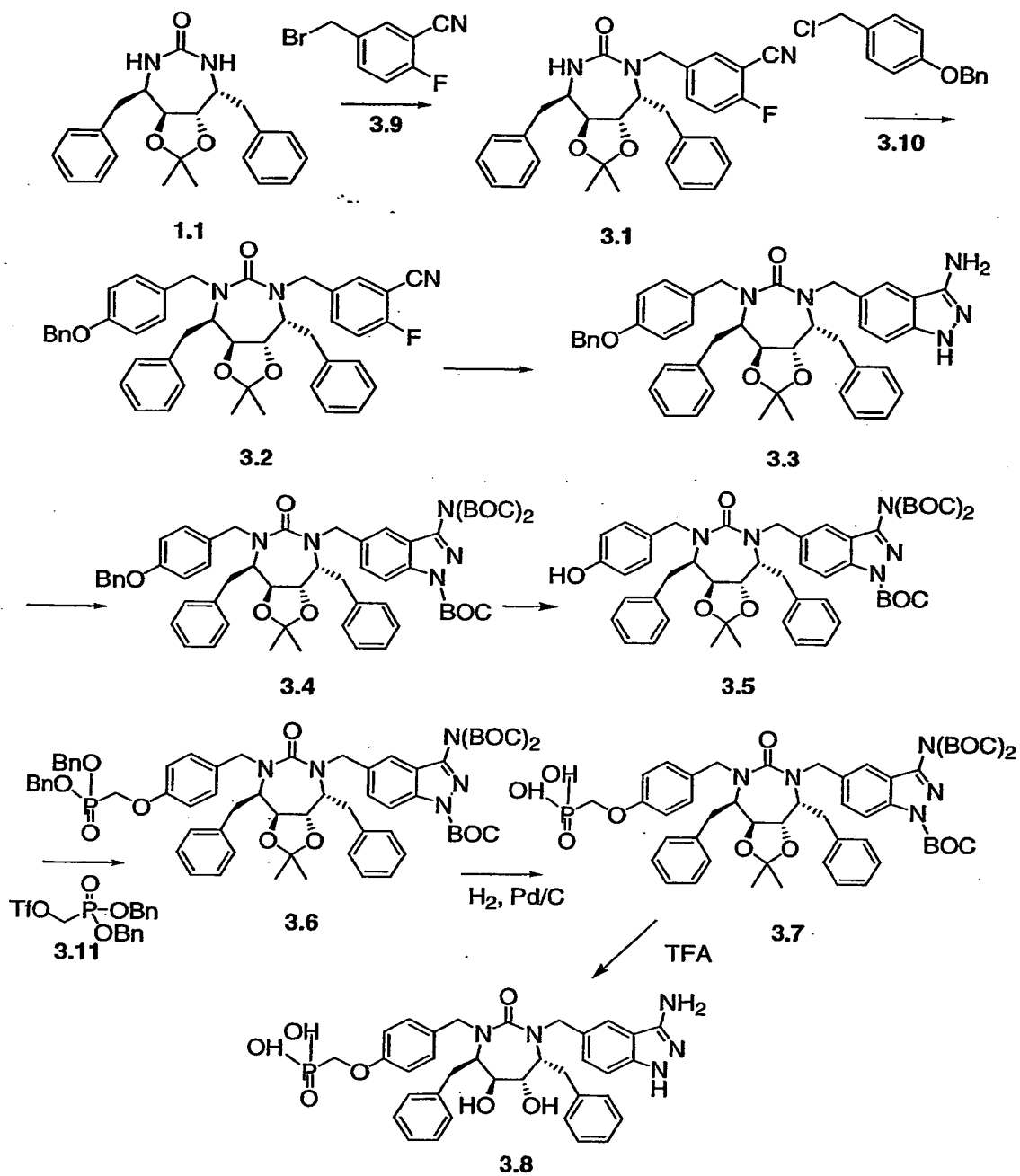
3-Cyano-4-fluorobenzyl urea 3.1 : A solution of urea **1.1** (1.6 g, 4.3 mmol) in THF was treated with sodium hydride (0.5 g of 60 % oil dispersion, 13 mmol). The mixture was stirred at room temperature for 30 min and then treated with 3-cyano-4-fluorobenzyl bromide **3.9** (1.0 g, 4.8 mmol). The resultant solution was stirred at room temperature for 3 h,

5   concentrated under reduced pressure, and then partitioned between CH_2Cl_2 and saturated brine solution containing 1 % citric acid. The organic phase was separated , dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 15-25% ethyl acetate in hexanes to yield urea **3.1** (1.5 g, 69 %) as a white form.

10

Benzyl ether 3.2 : A solution of **3.1** (0.56 g, 1.1 mmol) in DMF (5 mL) was treated with sodium hydride (90 mg of 60 % oil dispersion, 2.2 mmol) and the resultant mixture stirred at room temperature for 30 min. 4-Benzyloxy benzyl chloride **3.10** (0.31 g, 1.3 mmol) was added and the resultant solution stirred at room temperature for 3 h. The mixture was

15   concentrated under reduced pressure and then partitioned between CH_2Cl_2 and saturated brine solution. The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel eluting with 1-10% ethyl acetate in hexanes to yield compound **3.2** (0.52 g, 67 %) as white form.

20   **Indazole 3.3**: Benzyl ether **3.2** (0.51 g, 0.73 mmol) was dissolved in n-butanol (10 mL) and treated with hydrazine hydrate (1 g, 20 mmol). The mixture was refluxed for 4 h and then allowed to cool to room temperature. The mixture was concentrated under reduced pressure and the residue was then partitioned between CH_2Cl_2 and 10 % citric acid solution. The organic phase was separated, concentrated under reduced pressure, and then purified by silica

25   gel column eluting with 5% methanol in CH_2Cl_2 to afford indazole **3.3** (0.42 g, 82 %) as white solid.

Boc-indazole 3.4 : A solution of indazole **3.3** (0.4 g, 0.59 mmol) in CH_2Cl_2 (10 mL) was treated with diisopropylethylamine (0.19 g, 1.5 mmol), DMAP (0.18 g, 1.4 mmol), and di-

30   tert-butyl dicarbonate (0.4 g, 2 mmol). The mixture was stirred at room temperature for 3 h and then partitioned between CH_2Cl_2 and 5 % citric acid solution. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The

residue was purified by silica gel eluting with 2% methanol in CH$_2$Cl$_2$ to afford 3.4 (0.42 g, 71 %).

Phenol 3.5 : A solution of 3.4 (300 mg, 0.3 mmol) in ethyl acetate (10 mL) and methanol
(10 mL) was treated with 10 % Pd/C (40 mg) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield 3.5 as a white powder. This was used without further purification.

Dibenzyl ester 3.6 : A solution of 3.5 (0.1 mmol) in THF (5 mL) was treated with dibenzyl triflate 3.11 (90 mg, 0.2 mmol), and cesium carbonate (0.19 g, 0.3 mmol). The mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was partitioned between CH$_2$Cl$_2$ and saturated brine. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 20-40% ethyl acetate in hexanes to afford 3.6 (70 mg, 59 %). ^{1}H NMR (CDCl$_3$): δ 8.07 (d, 1H), 7.20-7.43 (m, 16H), 7.02-7.15 (m, 8 H), 6.80 (d, 2H), 5.07-5.18 (m, 4H), 5.03 (d, 1H), 4.90 (d, 1H), 4.20 (d, 2H), 3.74-3.78 (m, 4H), 3.20 (d, 1H), 3.05 (d, 1H) 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.40 (s, 18H), 1.26 (s, 6H); ^{31}P NMR (CDCl$_3$): 20.5 ppm.

Phosphonic acid 3.7: A solution of dibenzylphosphonate 3.6 (30 mg) in EtOAc (10 mL) was treated with 10% Pd/C (10 mg) and the mixture was stirred under a hydrogen atmosphere (balloon) for 3 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford phosphonic acid 3.7. This was used without further purification.

Phosphonic acid 3.8: The crude phosphonic acid 3.7 was dissolved in CH$_2$Cl$_2$ (2 mL) and treated with trifluoroacetic acid (0.4 mL). The resultant mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and then purified by preparative HPLC (35 % CH$_3$CN/65 % H$_2$O) to afford the phosphonic acid 3.8 (9.4 mg, 55 %). ^{1}H NMR (CD$_3$OD): δ 7.71 (s, 1H), 7.60 (d, 1H), 6.95-7.40 (m, 15H), 4.65 (d, 2H), 4.17 (d, 2H), 3.50-3.70 (m, 3H), 3.42 (d, 1H), 2.03-3.14 (m, 6H); ^{31}P NMR (CDCl$_3$): 17.30

-1539-

Scheme 4

4.1
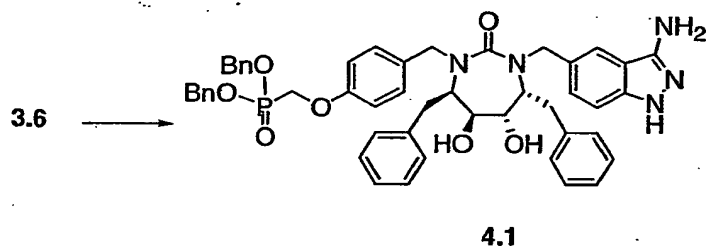
Dibenzylphosphonate 4.1: A solution of **3.6** (30 mg, 25 μmol) in CH₂Cl₂ (2 mL) was

5   treated with TFA (0.4 mL) and the resultant mixture was stirred at room temperature for 4 h.

The mixture was concentrated under reduced pressure and the residue was purified by silica

gel eluting with 50% ethyl acetate in hexanes to afford **4.1** (5 mg, 24%). ^{1}H NMR (CDCl₃): δ

6.96-7.32 (m, 25H), 6.95 (d, 2H), 5.07-5.18 (m, 4H), 4.86 (d, 1H), 4.7 5 (d, 1H), 4.18 (d, 2H),

3.40-3.62 (m, 4H), 3.25 (d, 1H), 2.80-3.15 (m, 6H); ^{31}P NMR (CDCl₃) 20.5 ppm; MS : 852

10 (M + H), 874 (M + Na).

Scheme 5

5.1

5.2

15
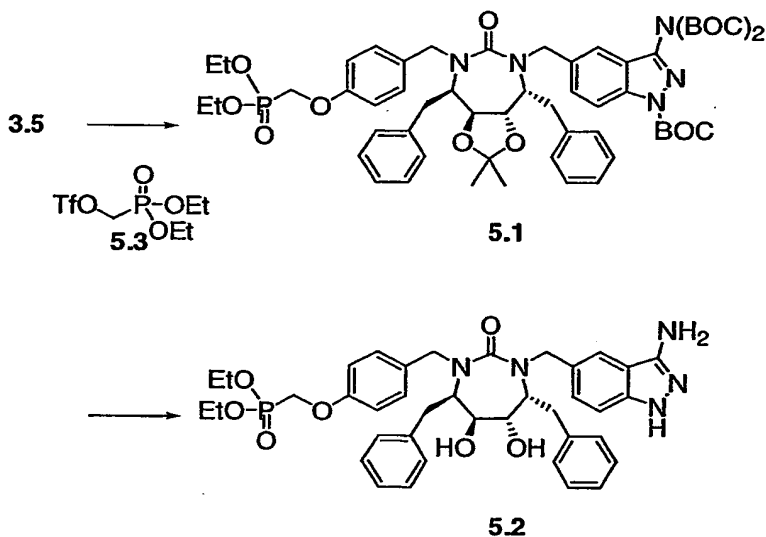
Diethylphosphonate 5.1: A solution of phenol **3.5** (48 mg, 52 μmol) in THF (5 mL) was

treated with triflate **5.3** (50 mg, 165 μmol), and cesium carbonate (22 mg, 0.2 mmol). The

resultant mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated brine. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 7% methanol in CH₂Cl₂

5   to afford **5.1** (28 mg, 50 %). ^{1}H NMR (CDCl₃): δ 8,06 (d, 1H), 7.30-7.43 (m, 7H), 7.02-7.30 (m, 7 H), 6.88 (d, 2H), 5.03 (d, 1H), 4.90 (d, 1H), 4.10-4.25 (m, 6H), 3.64-3.80 (m, 4H), 3.20 (d, 1H), 3.05 (d, 1H) 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.20-1.50 (m, 30H); ^{31}P NMR (CDCl₃): 18.5 ppm; MS :1068 (M + H), 1090 (M + Na).

10   **Diethylphosphonate 5.2:** A solution of **5.1** (28 mg, 26 µmol) in CH₂Cl₂ (2 mL) was treated with TFA (0.4 mL) and the resultant mixture was stirred at room temperature for 4 hrs. The mixture was concentrated under reduced pressure and the residue was purified by silica gel to afford **5.2** (11 mg, 55 %). ^{1}H NMR (CDCl₃ + 10 % CD₃OD): δ 6.96-7.35 (m, 15H), 6.82 (d, 2H), 4.86(d, 1H), 4.75 (d, 1H), 4.10-4.23 (M, 6H), 3.40-3.62 (m, 4H), 2.80-3.20 (m), 1.31 (t,

15   6 H); ^{31}P NMR (CDCl₃ + 10 % CD₃OD): 19.80 ppm; MS : 728 (M + H).

Scheme 6
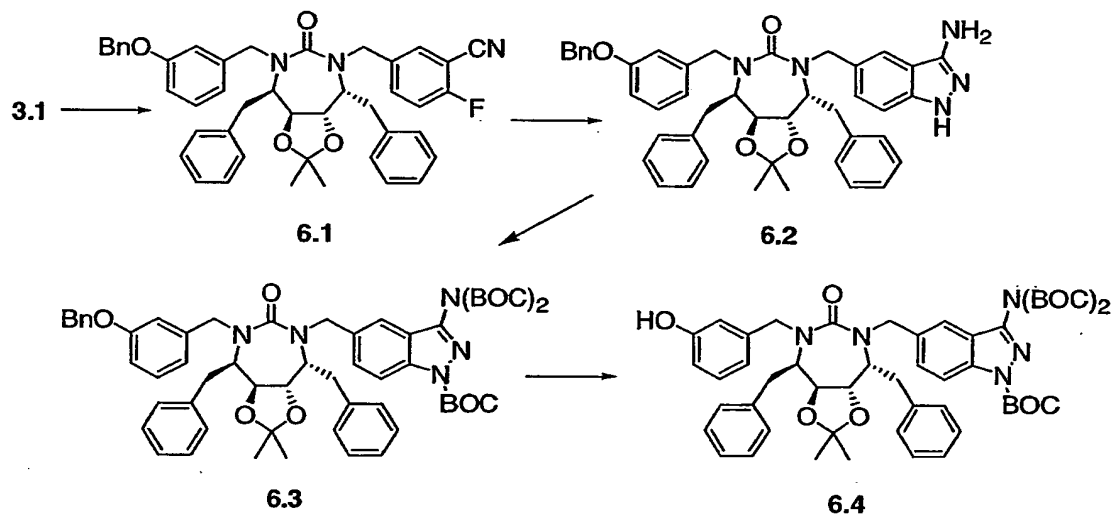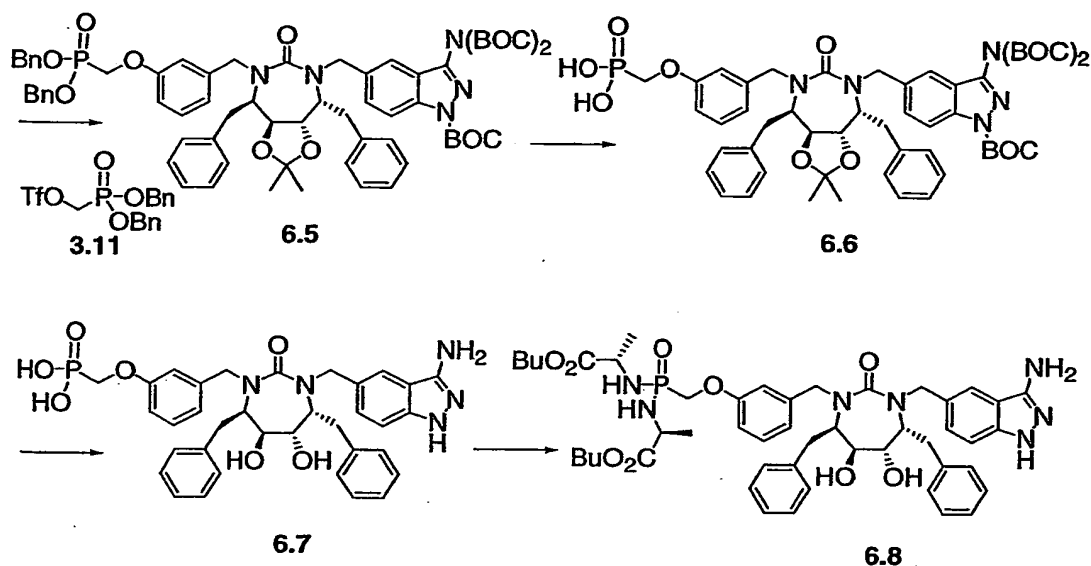
3-Benzyloxybenzyl urea 6.1 : The urea **3.1** (0.87 g, 1.7 mmol) was dissolved in DMF and treated with sodium hydride (60% dispersion, 239 mg, 6.0 mmol) followed by m-

5   benzyloxybenzylbromide **6.9** (0.60 g, 2.15 mmol). The mixture was stirred for 5 h and then diluted with ethyl acetate. The solution was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 25% ethyl acetate in hexanes to afford urea **6.1** (0.9 g, 75%).

10   **Indazole 6.2:** The urea **6.1** (41 mg, 59 μmol) was dissolved in n-butanol (1.5 mL) and treated with hydrazine hydrate (100 μL, 100 mmol). The mixture was refluxed for 2 h and then allowed to cool. The mixture was diluted with ethyl acetate, washed with 10% citric acid solution, brine, saturated NaHCO$_3$, and finally brine again. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude

15   product **6.2** (35 mg, 83%). (Chem. Biol. 1998, 5, 597-608).

Boc-indazole 6.3 : The indazole **6.2** (1.04 g, 1.47 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and treated with di-t-butyl dicarbonate (1.28 g, 5.9 mmol), DMAP (0.18 g, 1.9 mmol) and DIPEA (1.02 ml, 9.9 mmol). The mixture was stirred for 3 h and then diluted with ethyl

20   acetate. The solution was washed with 5% citric acid solution, NaHCO$_3$, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 50% ethyl acetate in hexanes to give **6.3** (0.71 g, 49%).

Phenol 6.4 : Compound **6.3** (20 mg, 0.021 mmol) was dissolved in MeOH (1 mL) and EtOAc (1 mL) and treated with 10% Pd/ C catalyst (5 mg). The mixture was stirred under a hydrogen atmosphere (balloon) until completion. The catalyst was removed by filtration and
5   the filtrate concentrated under reduced pressure to afford compound **6.4** (19 mg, 100%).

Dibenzyl phosphonate 6.5: A solution of compound **6.4** (0.34 g, 0.37 mmol) in acetonitrile (5 mL) was treated with Cs_2CO_3 (0.36 g, 1.1 mmol) and triflate **3.11** (0.18 mL, 0.52 mmol). The reaction mixture was stirred for 1 h. The reaction mixture was filtered and the filtrate
10   was then concentrated under reduced pressure. The residue was re-dissolved in EtOAc, washed with water, saturated $NaHCO_3$, and finally brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with hexane: EtOAc (1:1) to afford compound **6.5** (0.32 g, 73%).

15   **Phosphonic acid 6.6**: Compound **6.5** (208 mg, 0.174 mmol) was treated in the same manner as benzyl phosphonate **3.6** in the preparation of phosphonate diacid **3.7**, except MeOH was used as the solvent, to afford compound **6.6** (166 mg, 94%).

Phosphonic acid 6.7: Compound **6.6** (89 mg, 0.088 mmol) was treated according to the
20   conditions described in Scheme 3 for the conversion of **3.7** into **3.8**. The residue was purified by preparative HPLC eluting with a gradient of 90% methanol in 100 mM TEA bicarbonate buffer and 100% TEA bicarbonate buffer to afford phosphonic acid **6.7** (16 mg, 27%)

Bisamidate 6.8 : Triphenylphosphine (112 mg, 0.43 mmol) and aldrithiol-2 (95 mg, 0.43
25   mmol) were mixed in dry pyridine (0.5 mL). In an adjacent flask the diacid **6.7** (48 mg, 0.71 mmol) was suspended in dry pyridine (0.5 mL) and treated with DIPEA (0.075 mL 0.43 mmol) and L-AlaButyl ester hydrochloride (78 mg, 0.43 mmol) and finally the triphenylphosphine, aldrithiol-2 mixture. The reaction mixture was stirred under nitrogen for 24 h then concentrated under reduced pressure. The residue was purified by preparative
30   HPLC eluting with a gradient of 5% to 95% acetonitrile in water. The product obtained was then further purified by silica gel eluting with CH_2Cl_2 : MeOH (9:1) to give compound **6.8** (9 mg, 14%).

Scheme 7

7.1   **7.2**
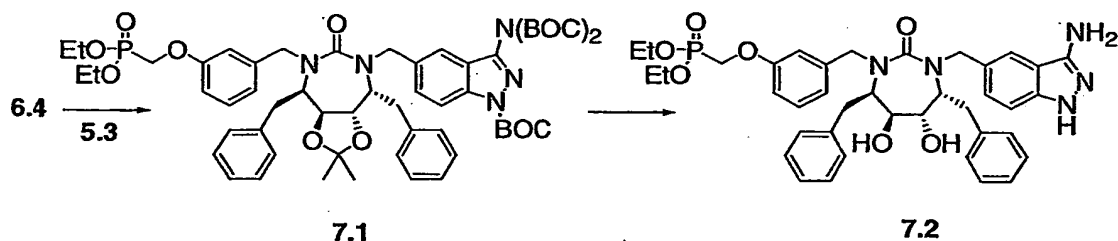
5   **Diethyl phosphonate 7.1** : Compound **6.4** (164 mg, 0.179 mmol) was treated according to
the procedure used to generate compound **6.5** except triflate **5.3** was used in place of triflate
3.11 to afford compound **7.1** (142 mg, 74%).

Diethylphosphonate 7.2 : Compound **7.1** (57 mg, 0.053 mmol) was treated according to the
10   conditions used to form **6.7** from **6.6**. The residue formed was purified by silica gel eluting
with CH$_2$Cl$_2$: MeOH (9:1) to afford compound **7.2** (13 mg, 33%).

Scheme 8

8.1   **8.2**

8.3   **8.4**
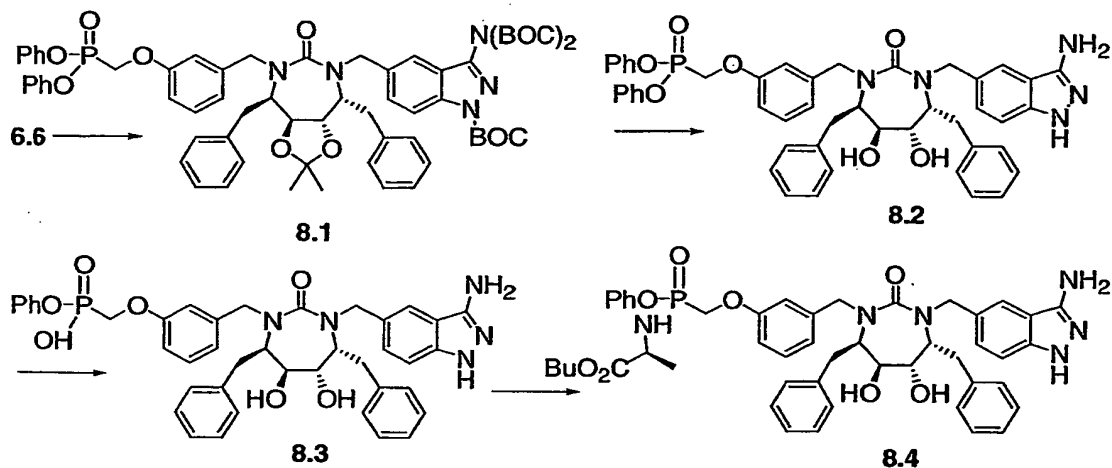
Diphenylphosphonate 8.1: A solution of **6.6** (0.67g, 0.66 mmol) in pyridine (10 mL) was
treated with phenol (0.62 g, 6.6 mmol) and DCC (0.82 mg, 3.9 mmol). The resultant mixture
was stirred at room temperature for 5 min and then the solution was heated at 70°C for 3 h.
20   The mixture was allowed to cool to room temperature and then diluted with EtOAc and water

(2 mL). The resultant mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. The residue was triturated with CH_2Cl_2, and the white solid that formed was removed by filtration. The filtrate was concentrated under reduced pressure and the resultant residue was purified by silica gel eluting with 30% ethyl acetate in

5   hexanes to yield **8.1** (0.5 g, 65 %). ^{1}H NMR ($CDCl_3$): δ 8,08 (d, 1H), 7.41 (d, 1H), 7.05-7.35 (m, 22H), 6.85 (d, 2H), 6.70 (s, 1H). 5.19 (d, 1H), 5.10 (d, 1H), 4.70 (d, 2H), 3.70-3.90 (m, 4H), 3.20 (d, 1H), 3.11 (d, 1H), 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.40 (s, 18H), 1.30 (s, 6H); ^{31}P NMR ($CDCl_3$): 12.43 ppm

10   **Diphenylphosphonate 8.2** : A solution of **8.1** (0.5 g, 0.42 mmol) in CH_2Cl_2 (4 mL) was treated with TFA (1 mL) and the resultant mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and azeotroped twice with CH_3CN. The residue was purified by silica gel eluting with 5% methanol in CH_2Cl_2 to afford diphenylphosphonate **8.2** (0.25 g, 71 %). ^{1}H NMR ($CDCl_3$): δ 7.03-7.40 (m, 21H), 6.81-6.90

15   (m, 3H), 4.96 (d, 1H), 4.90 (d, 1H) 4.60-4.70 (m, 2H), 3.43-3.57 (m, 4H), 3.20 (d, 1H), 2.80-2.97 (m, 5H); ^{31}P NMR ($CDCl_3$): 12.13 ppm; MS : 824 (M + H).

Monophenol 8.3 : The monophenol **8.3** (124 mg, 68 %) was prepared from the diphenol **8.2** by treating with 1N NaOH in acetonitrile at 0°C.

20

Monoamidate 8.4 : To a pyridine solution (0.5 mL) of **8.3** (40 mg, 53 μmol), n-butyl amidate HCl salt (116 mg, 640 μmol), and DIPEA (83 mg, 640 μmol) was added a pyridine solution (0.5 mL) of triphenyl phosphine (140 mg, 640 μmol), and aldrithiol-2 (120 mg, 640 μmol). The resulting solution was stirred at 65°C overnight, worked up, and purified by

25   preparative TLC twice to give **8.4** (1.8 mg). δ 4.96 (d, 1H), 4.90 (d, 1H) 4.30-4.6 (m, 2H), 3.9-4.2 (m, 2H), 3.6-3.70 (m, 4H), 3.2-3.3 (d, 1H), 2.80-3.1 (m, 4H); MS: 875 (M + H) & 897 (M + Na)

Scheme 9

9.1
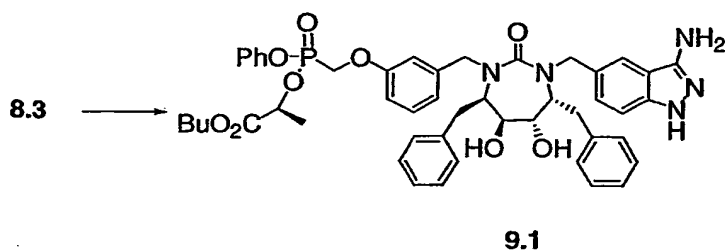
5   Monolactate **9.1**: The monolactate **9.1** is prepared from **8.3** using the conditions described
     above for the preparation of the monoamidate **8.4** except n-butyl lactate was used in place of
     n-butyl amidate HCl salt.

Scheme 10

10

10.1

10.2
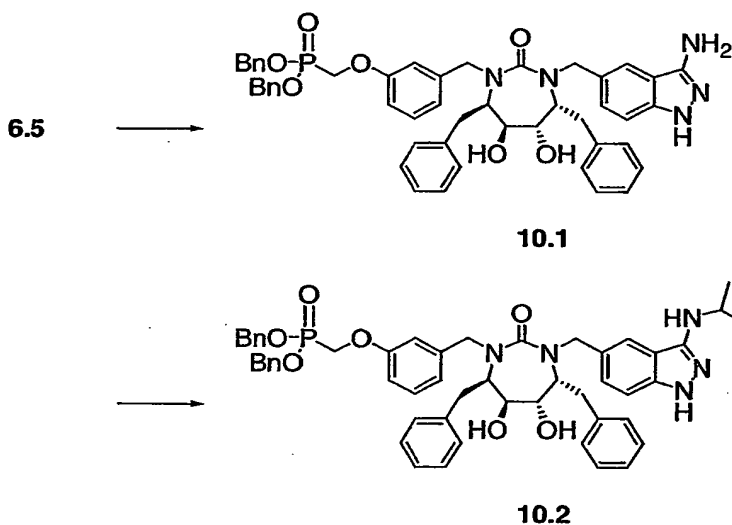
Dibenzylphosphonate 10.1: Compound **6.5** (16 mg, 0.014 mmol) was dissolved in CH_2Cl_2
(2 mL) and cooled to 0°C. TFA (1 mL) was added and the reaction mixture was stirred for
15   0.5 h. The mixture was then allowed to warm to room temperature for 2 h. The reaction
mixture was concentrated under reduced pressure and azeotroped with toluene. The residue
was purified by silica gel eluting with CH_2Cl_2 : MeOH (9:1) to afford compound **10.1** (4 mg,
32%).

Isopropylamino indazole 10.2 : Compound **10.1** (30 mg, 0.35 mmol) was treated with
acetone according to the method of Henke et al. (J. Med Chem. 40 17 (1997) 2706-2725) to
yield **10.2** as a crude residue. The residue was purified by silica gel eluting with CH₂Cl₂ :
MeOH (93:7) to afford compound **10.2** (3.4 mg, 10%).

5

Scheme 11

11.8 → **11.9**

11.9 → **11.10** → **11.11**

5.3

11.4 TfO⌒PO₃Et₂ → **11.12** TFA →

11.13
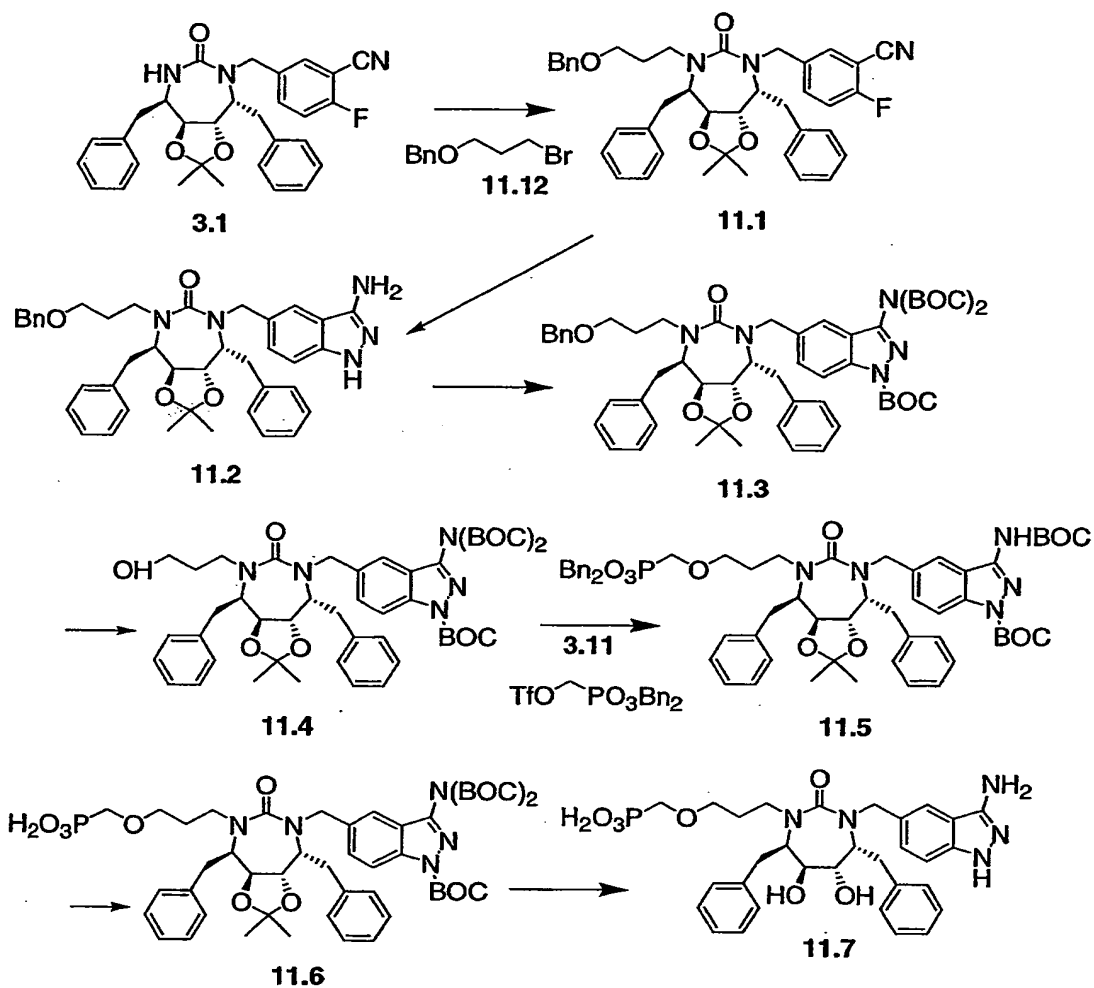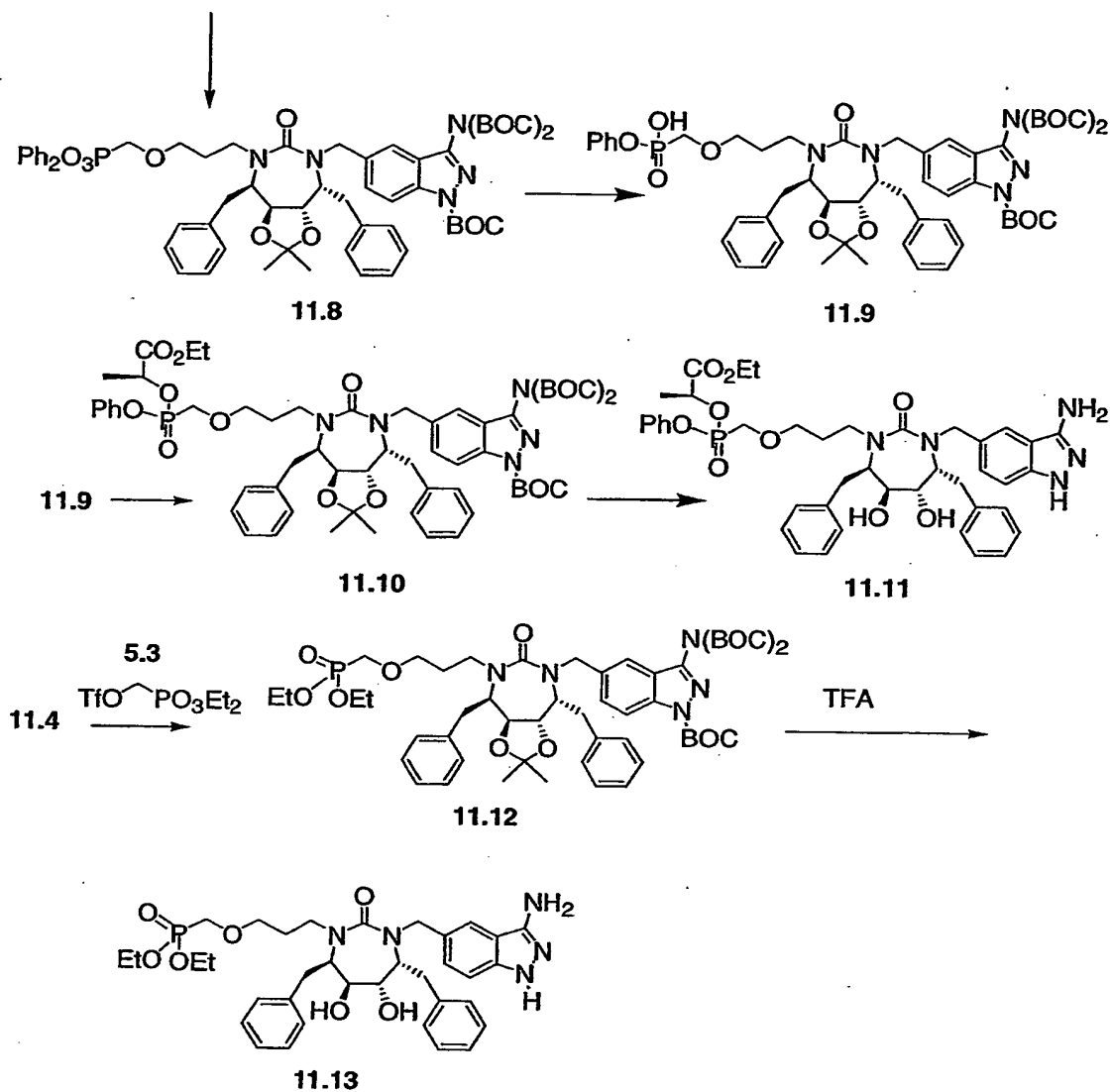
Benzyl ether 11.1: A DMF solution (5 mL) of **3.1** (0.98 g, 1.96 mmol) was treated with NaH
(0.24 g of 60 % oil dispersion, 6 mmol) for 30 min, followed by the addition of sodium
iodide (0.3 g, 2 mmol), and benzoxypropyl bromide (0.55 g, 2.4 mmol). After the reaction
for 3 h at room temperature, the reaction mixture was partitioned between methylene chloride
and saturated NaCl, dried, and purified to give **11.1** (0.62 g, 49 %).

Aminoindazole 11.2: A n-butanol solution (10 mL) of **11.1** (0.6 g, 0.92 mmol) and
hydrazine hydrate (0.93 g, 15.5 mmol) was heated at reflux for 4 h. The reaction mixture was
concentrated under reduced pressure to give crude **11.2** (~0.6 g).

Tri-BOC-Aminoindazole 11.3: A methylene chloride solution (10 mL) of crude **11.2**, DIPEA (0.36 g, 2.8 mmol), (BOC)₂O (0.73 g, 3.3 mmol), and DMAP (0.34 g, 2.8 mmol) was stirred for 5 h at room temperature, partitioned between methylene chloride and 5 % citric

5   acid solution, dried, purified by silica gel column chomatography to give **11.3** (0.51 g, 58 %, 2 steps).

3-Hydroxypropyl cyclic urea 11.4: An ethyl acetate/ethanol solution (30 mL/5 mL) of **11.3** (0.5 g, 0.52 mmol) was hydrogenated at 1 atm in the presence of 10 % Pd/C (0.2 g) for 4 h.

10   The catalyst was removed by filtration. The filtrate was then concentrated under reduced pressure to afford crude **11.4** (0.44 g, 98 %).

Dibenzyl phosphonate 11.5: A THF solution (3 mL) of **11.4** (0.5 g, 0.57 mmol) and triflate dibenzyl phosphonate **3.11** (0.37 g, 0.86 mmol) was cooled to –3°C, followed by addition of

15   n-BuLi (0.7 mL of 2.5 M hexane solution, 1.7 mmol). After 2 h reaction, the reaction mixture was partitioned between methylene chloride and saturated NaCl solution, concentrated under reduced pressure. The residue was redissolved in methylene chloride (10 mL), and reacted with (BOC)₂O (0.15 g, 0.7 mmol) in the presence of DMAP (0.18 g, 0.57 mmol), DIPEA (0.18 g, 1.38 mmol) for 2 h at room temperature. The reaction mixture was

20   worked up, and purified by silica gel chromatography to give **11.5** (0.25 g, 43 %).

Phosphonic diacid 11.7: An ethyl acetate solution (2 mL) of **11.5A** (11 mg, 10.5 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (10 mg) for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give crude

25   **11.6**. The crude **11.6** was redissolved in methylene chloride (1 mL) and treated with TFA (0.2 mL) for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by HPLC to give **11.7** (2 mg, 30%).
NMR (CD₃OD): δ 7.1-7.3 (m, 11H), 7.0-7.1 (d, 2H), 4.95 (d, 1H), 3.95-4.1 (d, 1H), 2.9 -3.3 (m, 4H), 2.3-2.45 (m, 1H), 1.6-1.8 (m, 2H). P NMR (CD₃OD):15.5 ppm. MS: 624 (M + 1).

30

Diphenyl phosphonate 11.8: A pyridine solution (1 mL) of **11.6** (0.23 g, 0.23 mmol), phenol (0.27 g, 2.8 mmol), and DCC (0.3 g, 1.4 mmol) was stirred for 5 min. at room temperature, then reacted at 70°C for 3 h. The reaction mixture was cooled to room

temperature, concentrated under reduced pressure, and purified by silica gel column chromatograph to afford **11.8** (0.11g, 41 %).

Monophenyl phosphonate 11.9: An acetonitrile solution (2 mL) of **11.8** (0.12 g, 0.107 mmol) at 0°C was treated with 1N sodium hydroxide aqueous solution (0.2 mL) for 1.5 h., then acidified with Dowex (50wx8-200, 120 mg). The Dowex was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was triturated with 10 % EtOAc/90 % hexane twice to afford **11.9** (90 mg, 76 %) as a white solid .

Mono-ethyl lactate phosphonate 11.10: A pyridine solution (0.3 mL) of **11.9** (33 mg, 30 µmol), ethyl lactate (41 mg, 340 µmol), and DCC (31 mg, 146 µmol) was stirred at room temperature for 5 min, then reacted at 70°C for 1.5 h. The reaction mixture was concentrated under reduced pressure, partitioned between methylene chloride and saturated NaCl solution, and purified by silica gel chromatography to give **11.10** (18 mg, 50 %).

Ethyl lactate phosphonate 11.11: A methylene chloride solution (0.8 mL) of **11.10** (18 mg, 15.8 µmol) was treated with TFA (0.2 mL) for 4 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **11.11** (6 mg, 50 %). NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.0-7.3 (m, 16 H), 6.8-7.0 (m, 2H), 4.9-5.0 (m, 1H), 4.75 (d, 1H), 4.1-4.2 (m, 2H). 3.5-4.0 (m, 10H), 2.18-2.3. (m, 1H), 1.6-1.7 (m, 1), 1.47 & 1.41 (2d, 3H), 1.22 (t, 3H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 19.72 & 17.86 ppm.

Diethyl phosphonate 11.13: Compound **11.13** (6 mg) was prepared as described above in Scheme 5 from **11.4** (30 mg, 34 µmol) and triflate phosphonate **5.3** (52 mg, 172 µmol), followed by TFA treatment. NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.1-7.32 (m, 11 H), 6.9-7.0 (d, 2H), 4.75 (d, 1H), 4.1-4.2 (2q, 4H), 3.84-3.9 (m, 1H), 3.4-3.8 (m, 8H), 2.7-3.1 (m, 4H), 2.1-2.5 (m, 1H), 1.5-1.7 (m, 2H), 1.25-1.35 (2t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 21.63 ppm. MS: 680 (M + 1).

Scheme 12

11.9 ⟶ **12.1** ⟶ **12.2**
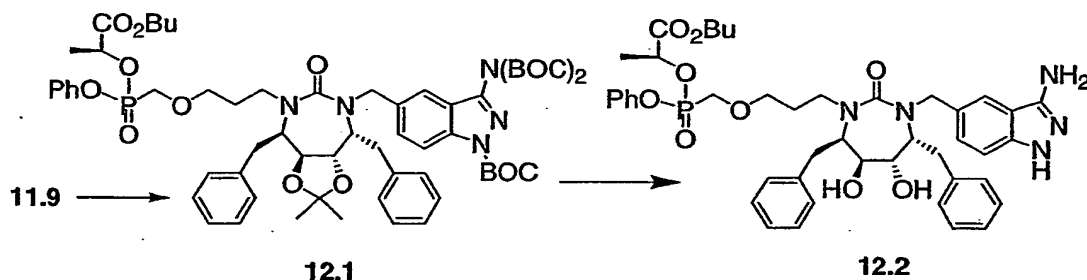
5   **Butyl lactate phosphonate 12.2:** A pyridine solution (0.3 mL) of **11.9** (27 mg, 22 µmol),
butyl lactate (31 mg, 265 µmol), and DCC (28 mg, 132 µmol) was stirred at room
temperature for 5 min, then reacted at 70°C for 1.5 h. The reaction mixture was concentrated
under reduced pressure, partitioned between methylene chloride and saturated NaCl solution,
and purified by preparative TLC to give **12.1** (12 mg). A methylene chloride solution (0.8

10   mL) of **12.1** (12 mg) was treated with TFA (0.2 mL) for 4 h, concentrate. The residue was
purified by preparative TLC to give **12.2** (3 mg, 16 %). NMR (CDCl₃ + ~10 %CD₃OD): δ
6.8-7.4 (m, 18H), 6.4-6.6 (m), 4.9-5.05 (m, 1H), 4.75 (d, 1H), 4.1-4.2 (m, 2H). 3.5-4.0 (m,
10H), 3.1-3.25 (m, 2H), 2.2-2.35 (m, 1H), 1.8-1.9 (m, 1H), 1.4 & 1.8 (m, 7H), 1.22 (t, 3H). P
NMR (CDCl₃ + ~10 %CD₃OD): 19.69 & 17.86 ppm.

Scheme 13

3.1 → **13.1**

BnO⌒⌒Br

13.2 → **13.3**

13.4 → **13.5**

13.6
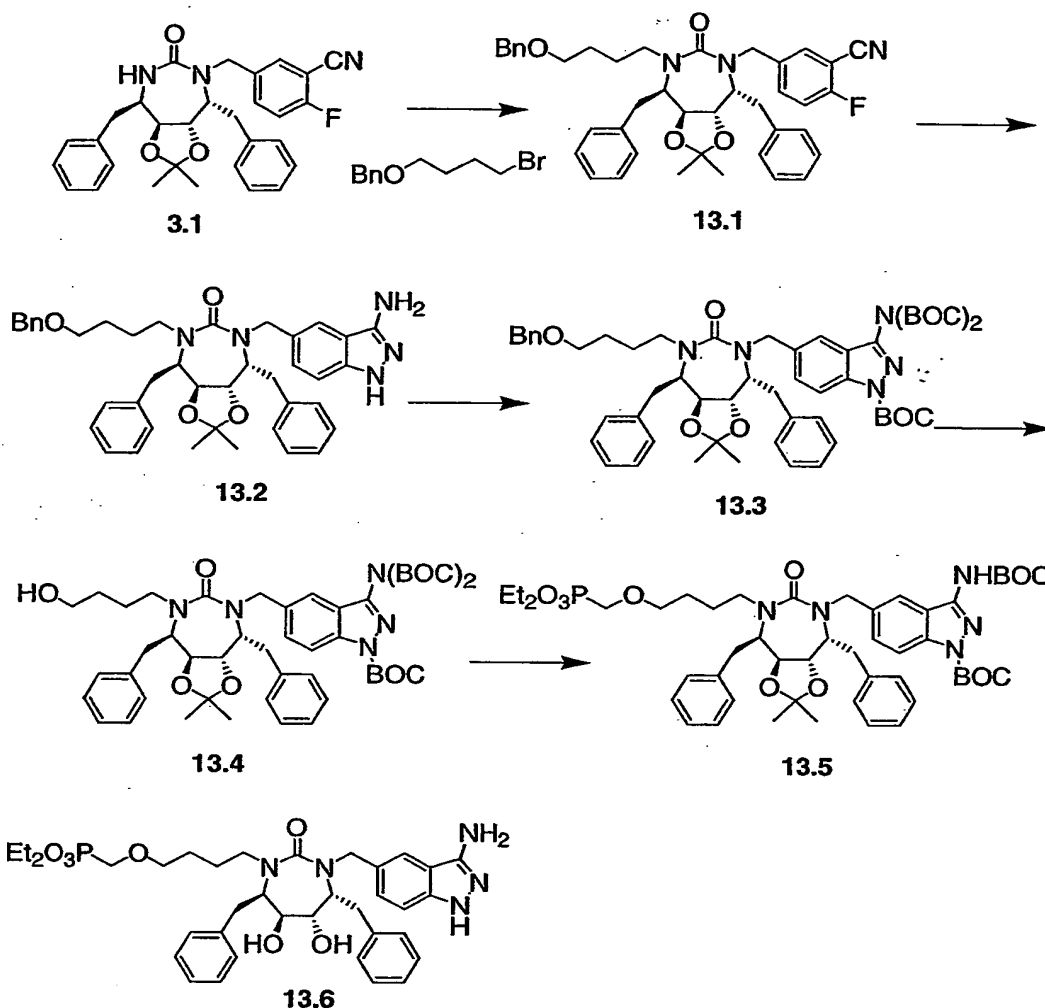
Benzyl ether 13.1: A DMF solution (5 mL) of **3.1** (1 g, 2 mmol) was treated with NaH (0.24 g of 60% oil dispersion, 6 mmol) for 30 min, followed by the addition of sodium iodide (0.3 g, 2 mmol),and benzoxybutyl bromide (0.58 g, 2.4 mmol). After the reaction for 5 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give **13.1** (0.58 g, 44 %).

Aminoindazole 13.2: A n-butanol solution (10 mL) of **11.1** (0.58 g, 0.87 mmol) and hydrazine hydrate (0.88 g, 17.5 mmol) was heated at reflux for 4 h. The reaction mixture was concentrated under reduced pressure to give crude **13.2** (0.56 g).

Tri-BOC-aminoindazole 13.3: A methylene chloride solution (10 mL) of **13.2** (0.55 g, 0.82 mmol), DIPEA (0.42 g, 3.2 mmol), (BOC)$_2$O (0.71 g, 3.2 mmol), and DMAP (0.3 g, 2.4 mmol) was stirred for 4 h at room temperature, partitioned between methylene chloride and 5% citric acid solution, dried, purified by silica gel chromatography to give **13.3** (0.56 g, 71 %, 2 steps).

3-Hydroxybutyl cyclic urea 13.4: An ethyl acetate/methanol solution (30 mL/5 mL) of **11.3** (0.55 g, 0.56 mmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (0.2 g) for 3 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford crude **13.4** (0.5 g, 98 %).

Diethyl phosphonate 13.6: A THF solution (1 mL) of **13.4** (5 mg, 56 μmol) and triflate diethyl phosphonate **5.3** (30 mg, 100 μmol) was cooled to –3°C, followed by addition of n-BuLi (80 μl of 2.5 M hexane solution, 200 μmol). After 2 h reaction, the reaction mixture was partitioned between methylene chloride and saturated NaCl solution, concentrated under reduced pressure to give crude **13.5**. The residue was dissolved in methylene chloride (0.8 mL) and treated with TFA (0.2 mL) for 4 h. concentrated under reduced pressure, and purified by HPLC to give **13.6** (8 mg, 21%). NMR (CDCl$_3$): δ 7.1-7.4 (m, 11H), 7.0-7.1 (m, 2H) 4.81 (d, 1H), 4.1-4.25 (m, 4H). 3.85-3.95 (m, 1H), 3.4-3.8 (m, 7H), 3.3-3.4 (m, 1H), 2.8 - 3.25 (m, 5H), 2.0-2.15 (m, 1H), 1.3-1.85 (m, 10H). P NMR (CDCl$_3$): 21.45 ppm.

Scheme 13a

13.7

1. H$_2$, 10% Pd/C

2. TFA

13.8
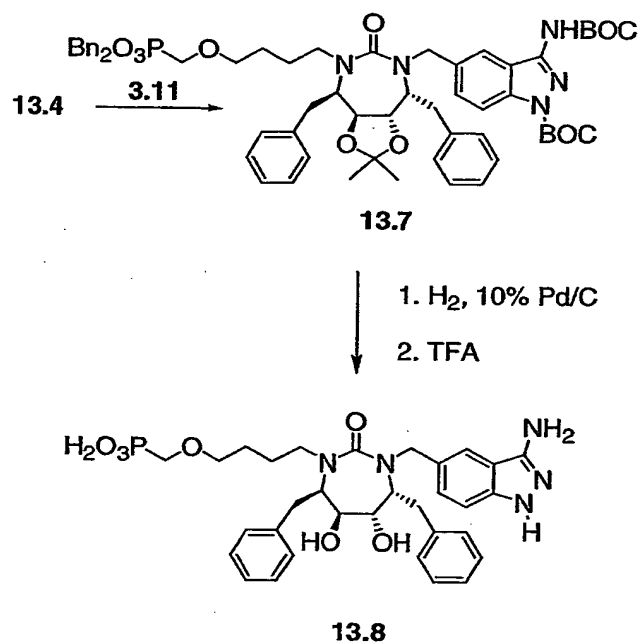
5   **Phosphonic diacid 13.8**: Compound **13.8** (4.5 mg) was prepared from **13.4** as described
     above for the preparation of **11.7** from **11.4** (Scheme 11). NMR (CD$_3$OD): δ 7.41 (s, 1H),
     7.1-7.4 (m, 10H), 6.9-7.0 (m, 2H) 4.75 (d, 1H), 3.8-4.0 (m, 1H). 3.4-3.8 (m, 8H), 2.8 -3.25
     (m, 5H), 2.1-2.25 (m, 1H), 1.6-1.85 (m, 4H). MS: 638 (M + 1).

Scheme 14
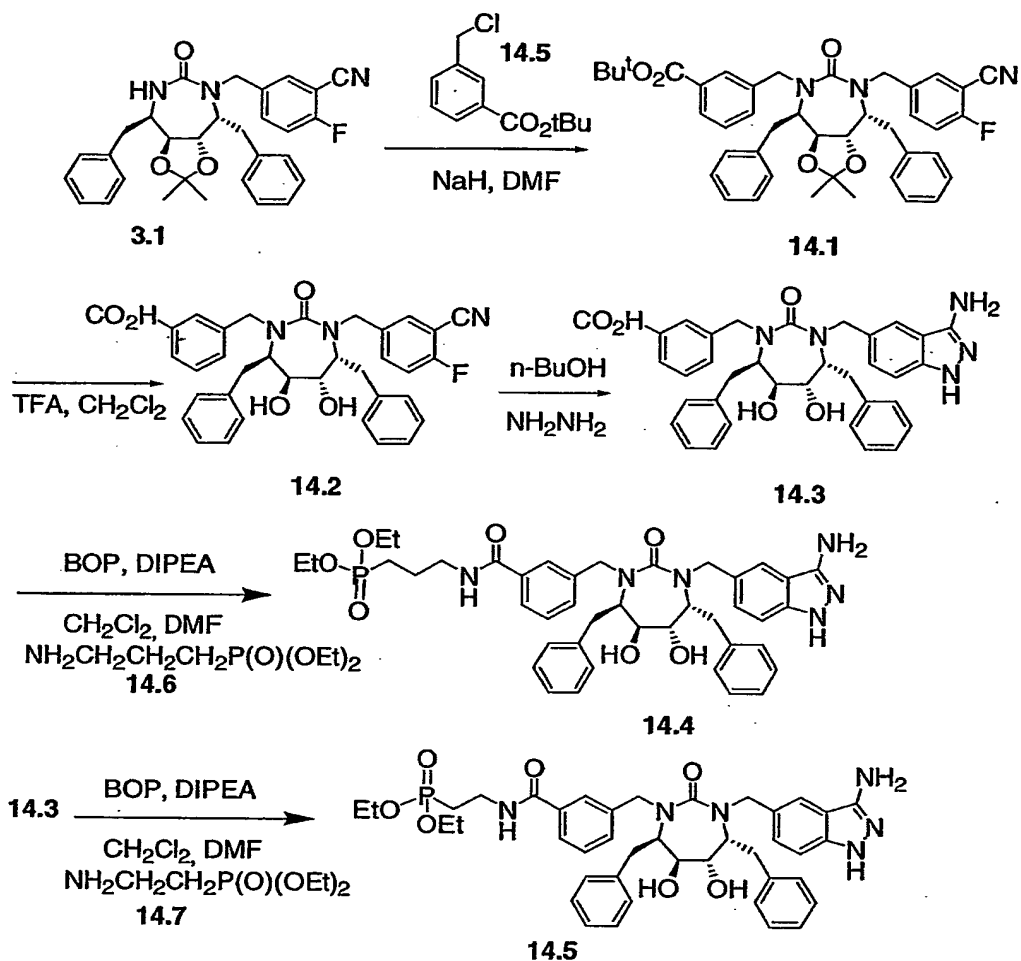
5   **t-Butyl ester 14.1:** A DMF solution (3 mL) of **3.1** (0.5 g, 1 mmol) was treated with NaH (80
mg of 60% oil dispersion, 2 mmol) for 10 min, followed by the addition of **14.5** (0.25 g, 1.1
mmol). After the reaction for 1 h at room temperature, the reaction mixture was partitioned
between methylene chloride and saturated NaCl, dried, and purified to give **14.1** (0.4 g, 59%).

10   **Aminoindazole derivative 14.3:** A methylene chloride solution (5 mL) of **14.1** (0.4 g, 0.58
mmol) was treated with TFA (1 mL) at room temperature for 1.5 h, and then concentrated
under reduced pressure to give crude **14.2**. The crude **14.2** was dissolved in n-BuOH (5 mL)
and reacted with hydrazine hydrate (0.58 g, 11.6 mmol) at reflux for 5 h. The reaction

mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the desired product **14.3** (0.37 g, quantitative yield).

5 **Diethylphosphonate ester 14.4**: A methylene chloride solution (3 mL) of **14.3** (23 mg, 38 μmol) was reacted with aminopropyl-diethylphosphonate **14.6** (58 mg, 190 μmol), DIPEA (50 mg, 380 μmol), and ByBOP (21 mg, 48 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **14.4** (9 mg, 34 %). NMR (CDCl$_3$ + ~10 %CD$_3$O): δ 7.87 (t, 1H), 7.61 (b, 1H), 7.51 (s, 1H), 7.14-7.2 (m, 10 H), 6.93-
10 7.0 (m, 4H), 4.79 (d, 2H), 3.99-4.04 (m, 4H), 3.38-3.65 (m, 6H), 2.60-3.2 (m, 6 H), 1.70-1.87 (m, 4H), 1.25 (t, 6H). P NMR (CDCl$_3$ + ~10 %CD$_3$OD): 32.7 ppm.

Diethylphosphonate ester 14.5: A methylene chloride solution (2 mL) of **14.3** (13 mg, 21 μmol) was reacted with aminoethyl-diethylphosphonate oxalate **14.7** (23mg, 85 μmol),
15 DIPEA (22 mg, 170 μmol), and ByBOP (12 mg, 25 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give 14.5 (5mg, 30%). Ms: 783 (M + 1). NMR (CDCl$_3$ + ~10 %CD$_3$O): δ 7.88 (b, 1H), 7.58 (b, 1H), 7.49 (s, 1H), 7.14-7.2 (m, 10 H), 6.90-7.0 (m, 4H), 4.75 (d, 2H), 3.90-4.04 (m, 4H), 2.50-3.3 (m, 6 H), 1.97-
20 2.08 (m, 2H). P NMR (CDCl$_3$ + ~10 %CD$_3$OD): 30.12 ppm.
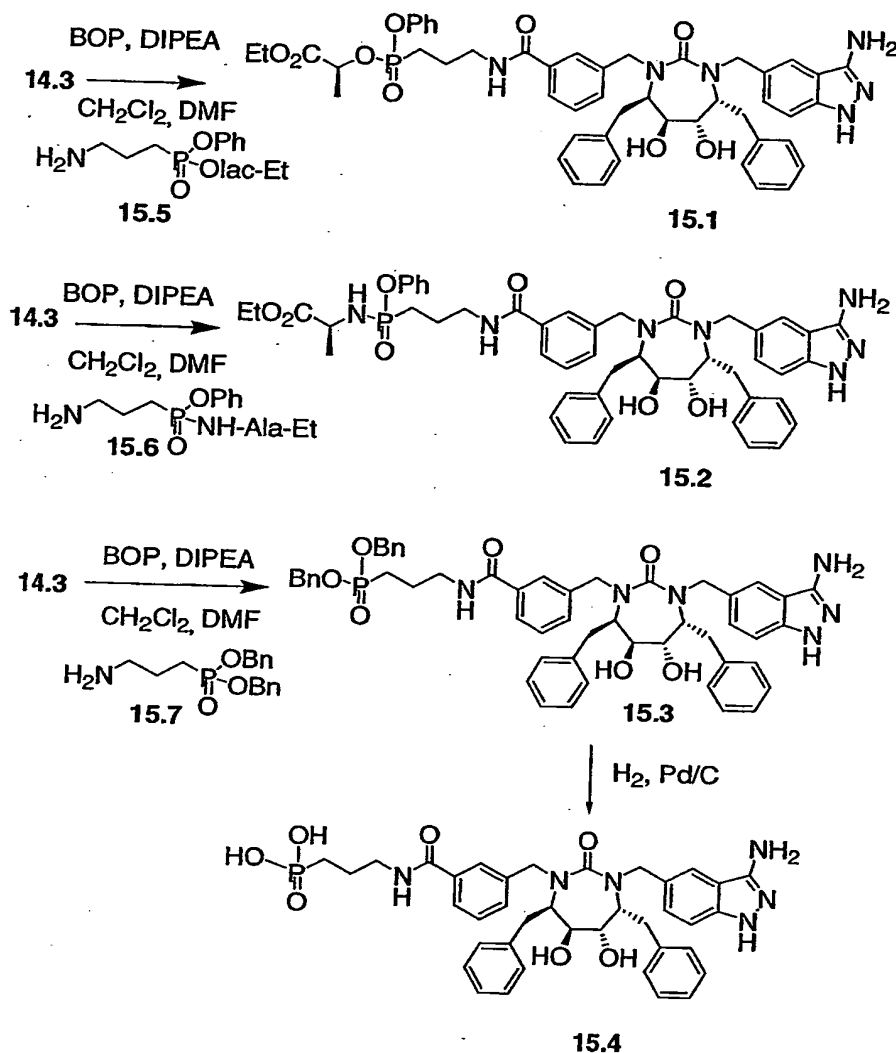
Scheme 15

Monophenol-ethyl lactate phosphonate prodrug 15.1: A methylene chloride/DMF
solution (2 mL/0.5 mL) of **14.3** (30 mg, 49 μmol) was reacted with aminopropyl-phenol-ethyl
lactate phosphonate **15.5** (100 mg, 233 μmol), DIPEA (64 mg, 495 μmol), and BOP reagent
(45 mg, 100 μmol) at room temperature for 2 h, and then concentrated under reduced
pressure. The residue was triturated with methylene chloride/hexane. The solid was purified
by silica gel chromatography to give **15.1** (28 mg, 64 %). NMR (CDCl₃ + ~10 %CD₃O): δ
7.83 (b, 1H), 7.59 (b, 1H), 7.51 (s, 1H), 7.14-7.2 (m, 11 H), 6.90-7.0 (m, 4H), 4.75-4.87 (d +

q, 3H), 4.10 (q, 2H), 3.3-3.61 (m, 6H), 2.60-3.2 (m, 6H), 1.92-2.12 (m, 4H), 1.30 (d, 3H),
1.18 (t, 3H). P NMR (CDCl₃ + ~10 %CD₃OD): 30.71 ppm. MS: 903 (M + 1).

Phenol-ethyl alanine phosphonate prodrug 15.2: A methylene chloride/DMF solution (2
mL/0.5 mL) of **14.3** (30 mg, 49 μmol) was reacted with aminopropyl-phenol-ethyl alanine
phosphonate **15.6** (80 mg TFA salt, 186 μmol), DIPEA (64 mg, 500 μmol), and BOP reagent
(45 mg, 100 μmol) at room temperature for 2 h, and then concentrated under reduced
pressure. The residue was triturated with methylene chloride/hexane. The solid was purified
by preparative TLC to give **15.2** (12 mg, 27 %). NMR (CDCl₃ + ~10 %CD₃O): δ 7.91 (b,
1H), 7.61 (b, 1H), 7.52 (s, 1H), 7.14-7.2 (m, 11 H), 6.90-7.0 (m, 4H), 4.75 (d, 2H), 3.82-4.1
(2q, 3H), 3.4-3.65 (m, 6H), 2.60-3.15 (m, 6H), 1.8-2.0 (m, 4H), 1.3 (d, 3H). P NMR (CDCl₃
+ ~10 %CD₃OD): 32.98 & 33.38 ppm. MS: 902 (M + 1).

Dibenzyl phosphonate 15.3: A methylene chloride/DMF solution (2 mL/0.5 mL) of **14.3**
(30 mg, 49 μmol) was reacted with aminopropyl dibenzyl phosphonate **15.7** (86 mg TFA
salt, 200 μmol), DIPEA (64 mg, 500 μmol), and BOP reagent (45 mg, 100 μmol) at room
temperature for 2 h, and then concentrated under reduced pressure. The residue was
triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give
15.3 (20 mg, 44%). NMR (CDCl₃ + ~5%CD₃O): δ 7.50-7.58 (m, 2H), 7.14-7.3 (m, 21 H),
6.90-7.0 (m, 4H), 4.7-5.1 (m, 6H), 3.6-3.8 (m, 4H), 3.3-3.55 (m, 2H), 2.60-3.15 (m, 6H), 1.8-
2.0 (m, 4H). P NMR (CDCl₃ + ~5 %CD₃OD): 33.7 ppm. MS: 907 (M + 1).

Phosphonic diacid 15.4: An ethanol solution (5 mL) of **15.3** (17 mg, 18.7 μmol) was
hydrogenated at 1 atm in the presence of 10 % Pd/C for 4 h. The catalyst was removed by
filtration, and the filtrate was concentrated under reduced pressure to give the desired product
15.4 (12 mg, 85%). NMR (CD₃O + 20%CDCl₃): δ 7.88 (b, 1H), 7.59 (b, 1H), 7.6 (s, 1H),
7.1-7.25 (m, 10 H), 6.90-7.1 (m, 4H), 4.8 (d, 2H + water peak), 3.6-3.8 (m, 4H), 3.4-3.5 (m,
2H), 1.85-2.0 (m, 4H).

Scheme 16
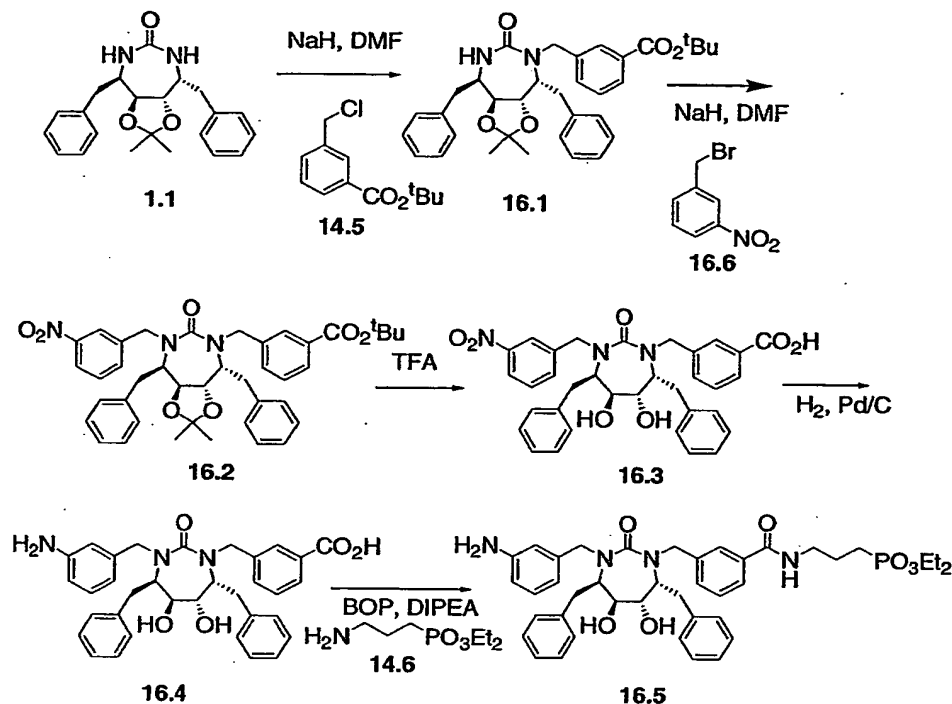
Monobenzyl derivative 16.1: A DMF solution (4 mL) of **1.1** (0.8 g, 2.2 mmol) was treated with NaH (0.18 g of 60% oil dispersion, 4.4 mmol) for 10 min at room temperature followed by the addition of **14.5** (0.5 g, 2.2 mmol). The resulting solution was reacted at room temperature for 2 h, worked up, and then purified to afford **16.1** (0.48 g, 40%).

3-Nitrobenzyl cyclic urea derivative 16.2: A DMF solution (0.5 mL) of **16.1** (65 mg, 117 μmol) was treated with NaH (15 mg of 60% oil dispersion, 375 μmol) for 10 min at room temperature, followed by the addition of 3-nitrobenzyl bromide (33 mg, 152 μmol). The resulting solution was reacted at room temperature for 1 h, worked up, and purified by preparative TLC to afford **16.2** (66 mg, 82%).

Diol 16.3: A methylene chloride solution (2 mL) of **16.2** (46 mg, 61 μmol) was treated with TFA (0.4 mL) for 2 h at room temperature, and then concentrated under reduced pressure to afford **16.3**. This material was used without further purification.

3-Aminobenzyl cyclic urea 16.4: An ethyl acetate/ethanol (5 mL/1 mL) solution of **16.3** (crude) was hydrogenated at 1 atm in the presence of 10% Pd/C for 2 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and purified by preparative TLC to afford **16.4** (26 mg, 70%, 2 steps).

5

Diethyl phosphonate 16.5: A methylene chloride/DMF solution (2 mL/0.5 mL) of **16.4** (24 mg, 42 μmol) was reacted with aminopropyl-diethylphosphonate ester TFA salt **14.6** (39 mg, 127 μmol), DIPEA (27 mg, 210 μmol), and BOP reagent (28 mg, 63 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was purified

10   by preparative TLC to give **16.5** (20.7 mg, 63 %). NMR (CDCl$_3$ + ~10 %CD$_3$O): δ 7.62 (b, 1H), 7.51 (s, 1H), 7.0-7.35 (m, 12 H), 6.95 (d, 2H), 6.85 (d, 2H), 4.6-4.71 (2d, 2H), 3.95-4.1 (m, 4H). 3.3-3.55 (m, 3H), 2.60-2.8 (m, 2H), 2.95-.3. 15 (m, 4 H), 1.85-2.0 (m, 4H), 1.25 (t, 6H). P NMR (CDCl$_3$ + ~10 %CD$_3$OD): 32.65 ppm.

Scheme 17

16.1 → (NaH, DMF; Cl—CH₂—C₆H₄—OBn **3.10**) → **17.1** → (TFA) →

17.2 → (H₂, 10% Pd/C) → **17.3**

14.6 → **17.4**
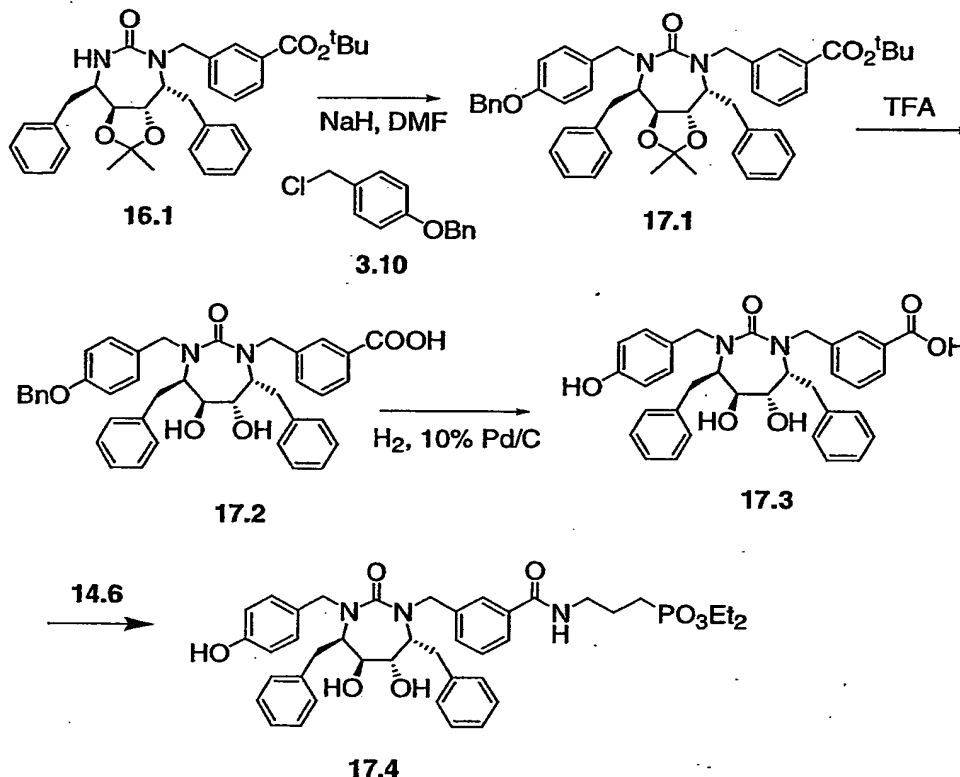
p-Benzoxybenzyl cyclic urea derivative 17.1: A DMF solution (0.5 mL) of **16.1** (65 mg, 117 μmol) was treated with NaH (15 mg of 60% oil dispersion, 375 μmol) for 10 min at room temperature, followed by the addition of 4-benzoxy benzyl chloride **3.10** (35 mg, μmol). The resulting solution was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure, purified by preparative TLC to generate **17.1** (62 mg, 70%).

Diethyl phosphonate 17.3: A methylene chloride solution (2 mL) of **17.1** (46 mg, 61 μmol) was treated with TFA (0.4 mL) for 2 h at room temperature, and then concentrated under reduced pressure to give crude **17.2**. An ethyl acetate/ethanol solution (3 mL/2 mL) of the crude **17.2** was then hydrogenated at 1 atm in the presence of 10% Pd/C (10 mg) for 5 h at room temperature. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford **17.3** (crude).

Diethyl phosphonate cyclic urea 17.4: A methylene chloride/DMF solution (2 mL/0.5 mL) of **17.3** (25 mg, 42 µmol) was reacted with aminopropyl-diethylphosphonate ester TFA salt **14.6** (40 mg, 127 µmol), DIPEA (27 mg, 210 µmol), and BOP reagent (28 mg, 63 µmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **17.4** (14.6 mg, 44 %). NMR (CDCl$_3$ + ~10 %CD$_3$O): δ 7.82 (t), 7.62 (d, 1H), 7.51 (s, 1H), 7.05-7.35 (m, 10 H), 6.8-6.95 (2d, 4H), 6.85 (d, 2H), 4.8 (d, 1H), 4.65 (d, 1H), 3.95-4.1 (m, 4H). 3.4-3.75 (m, 6H), 2.60-3.2 (m), 1.85-2.0 (m, 4H), 1.25 (t, 6H). P NMR (CDCl$_3$ + ~10 %CD$_3$OD): 32.72 ppm.

Scheme 18
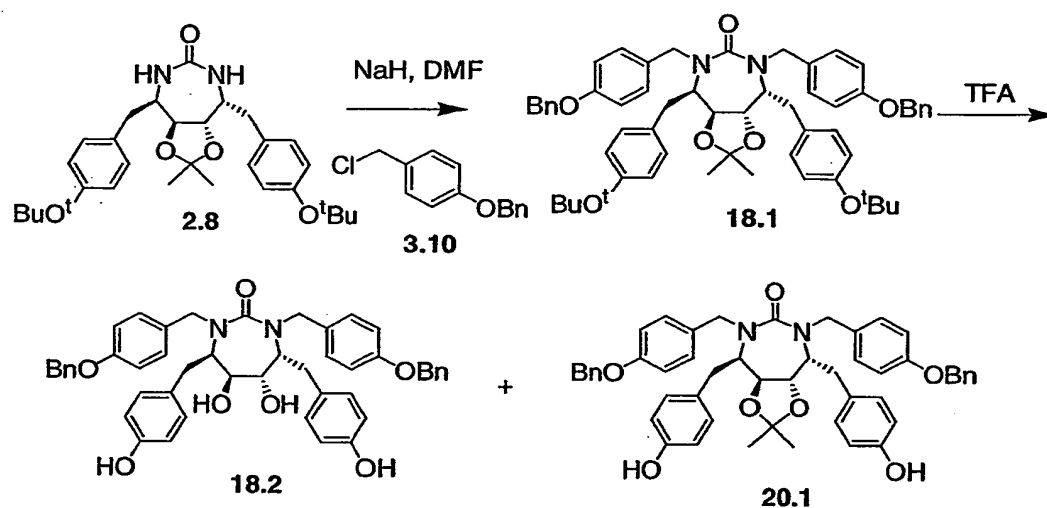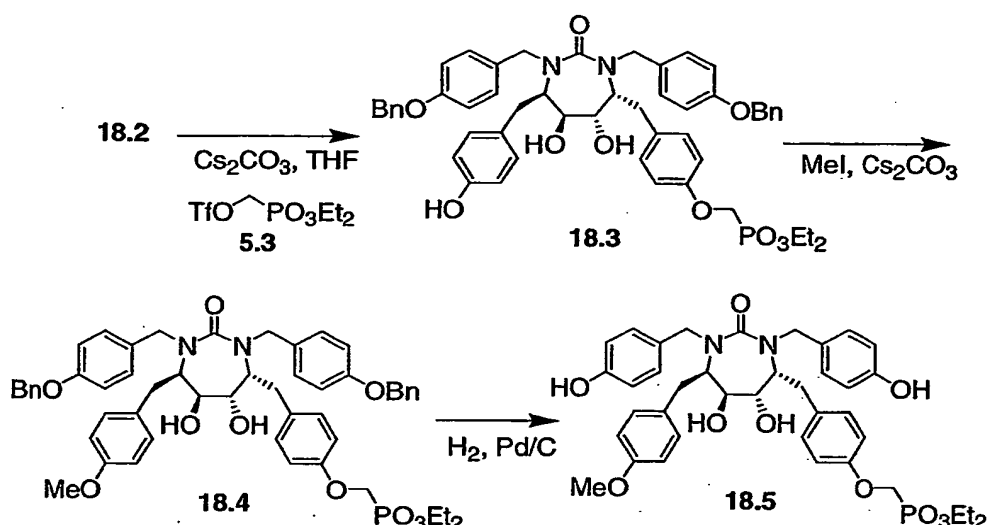
Dibenzyl derivative 18.1: A DMF solution (3 mL) of compound **2.8** (0.4 g, 0.78 mmol) was reacted with 60%NaH (0.13 g, 1.96 mmol), 4-benzoxy benzylchloride **3.10** (0.46 g, 1.96 mmol) and sodium iodide (60 mg, 0.39 mmol) at room temperature for 4 h. The reaction mixture was partitioned between methylene chloride and saturated NaHCO₃ solution. The organic phase was isolated, dried over Na₂SO₄, concentrated under reduced pressure, and purified by silica gel chromatography to give the desired product **18.1** (0.57 g, 81%).

Diol derivative 18.2 and diphenol derivative 20.1: A methylene chloride solution (4 mL) of **18.1** (0.57 g, 0.63 mmol) was treated with TFA (1 mL) at room temperature for 20 min, concentrated under reduced pressure, and purified by silica gel chromatography to give diol derivative **18.2** (133 mg, 28 %) and diphenol derivative **20.1** (288 mg. 57.6%).

Monophosphonate derivative 18.3: A THF solution (10 mL) of **18.2** (130 mg, 0.17 mmol) was stirred with cesium carbonate (70 mg, 0.21 mmol) and diethylphosphonate triflate **5.3** (52 mg, , 0.17 mmol) at room temperature for 4 h.. The reaction mixture was concentrated under reduced pressure and purified to give **18.3** (64 mg, 41 %), and recovered **18.2** (25 mg, 19%).

Methoxy derivative 18.4: A THF solution (2 mL) of **18.3** (28 mg, 25 μmol) was treated with cesium carbonate (25 mg, 76 μmol) and iodomethane (10 eq. Excess) at room

-1563-

temperature for 5 h. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated NaHCO$_3$. The organic phase was separated, concentrated under reduced pressure and the residue purified by preparative TLC to afford **18.4** (22 mg, 78%).

Diethylphosphonate 18.5 : An ethyl acetate/ethanol (2 mL/2 mL) solution of **18.4** (22 mg, 24 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C for 3 h. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure to give the desired product **18.5** (18 mg, quantitative). NMR (CDCl$_3$ + ~10 %CD$_3$O): δ 6.7-7.0 (m, 12 H), 6.62-6.69 (m, 4H), 4.65 (d, 1H), 4.50 (d, 1H), 4.18-4.3 (m, 6H). 3.75 (s, 3H), 3.3-3.4 (m, 4H), 2.8-3.0 (m, 6H), 1.30 (t, 6H). P NMR (CDCl$_3$ + ~10 %CD$_3$OD): 20.16 ppm.

Scheme 19
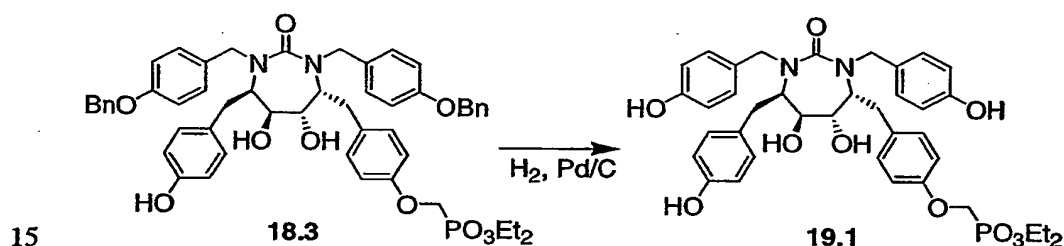
Diethyl phosphonate 19.1: An ethyl acetate/ethanol (2 mL/1 mL) solution of **18.3** (14 mg, 15.5 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (5 mg) for 3 h. The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **19.1** (10 mg, 90%). NMR (CDCl$_3$ + ~15 %CD$_3$O): δ 6.6-7.0 (m, 16 H), 4.5-4.65 (2d, 2H), 4.1-4.3 (m, 6H). 2.7-3.0 (m, 6H), 1.29 (t, 6H). P NMR (CDCl$_3$ + ~15 %CD$_3$OD): 20.12 ppm.

Scheme 20
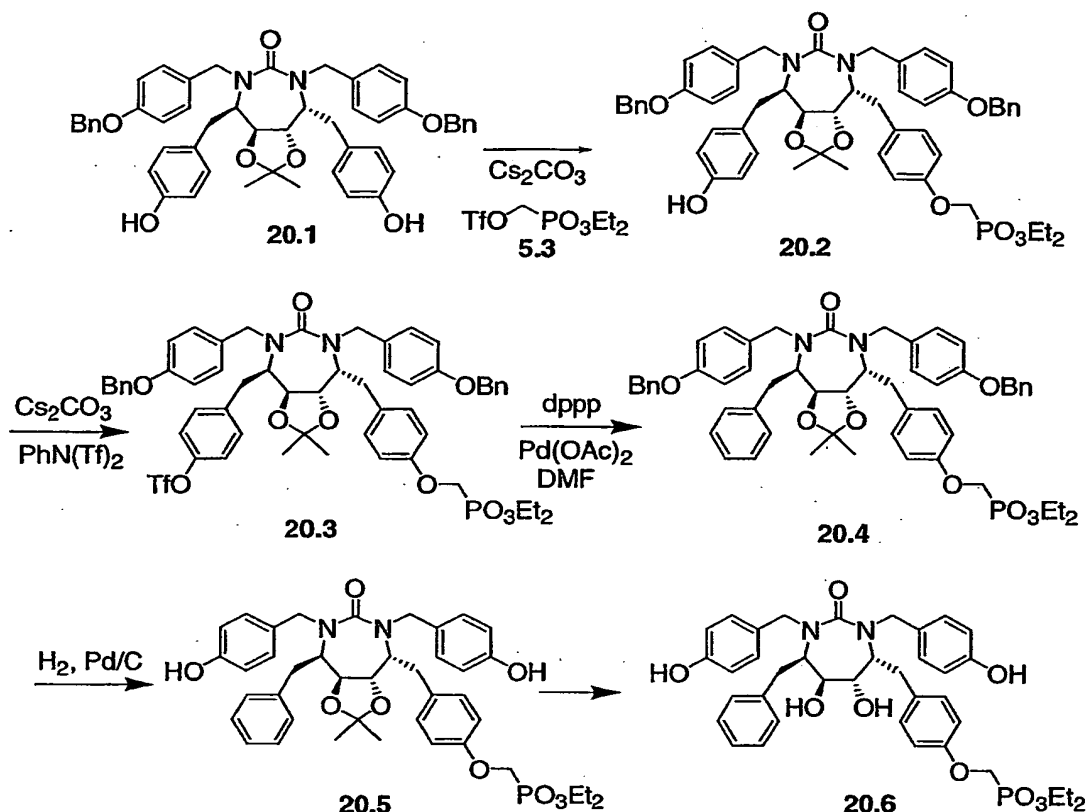
5   **Monophosphonate 20.2:** A THF solution (8 mL) of **20.1** (280 mg, 0.36 mmol) was stirred
with cesium carbonate (140 mg, 0.43 mmol) and diethylphosphonate triflate **5.3** (110 mg,
0.36 mmol) at room temperature for 4 h.. The reaction mixture was concentrated under
reduced pressure and purified to give **20.2** (130mg, 39%), and recovered **20.1** (76 mg, 27%).

10 **Triflate derivative 20.3:** A THF solution (6 mL) of **20.2** (130 mg, 0.13 mmol) was stirred
with cesium carbonate (67 mg, 0.21 mmol) and N-phenyltrifluoromethane-sulfonimide
(60mg, 0.17 mmol) at room temperature for 4 h. The reaction mixture was concentrated
under reduced pressure and purified to give **20.3** (125 mg, 84%).

15 **Benzyl ether 20.4:** To a DMF solution (2 mL) of Pd(OAc)₂ (60 mg, 267 µmol), and dppp
(105 mg. 254 µmol) was added **20.3** (120 mg, 111 µmol) under nitrogen, followed by the
addition of triethylsilane (0.3 mL). The resulting solution was stirred at room temperature for

4 h, then concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **20.4** (94 mg, 92%).

Diethyl phosphonate 20.6: An ethyl acetate/ethanol (2 mL/2 mL) solution of **20.4** (28 mg, 30 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (5 mg) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **20.5**. The crude product **20. 5** was redissolved in methylene chloride (2 mL) and treated with TFA (0.4 mL) and a drop of water. After 1 h stirring at room temperature, the reaction mixture was concentrated under reduced pressure, and purified by preparative TLC plate to give **20.6** (18 mg, 85 %, 2 steps). δ 6.6-7.3 (m, 17 H), 4.65 (d, 1H), 4.58 (d, 1H), 4.18-4.3 (m, 6H), 3.3-3.5 (m, 4H), 2.8-3.1 (m), 1.34 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 20.16 ppm. MS: 705 (M + 1).

Scheme 21
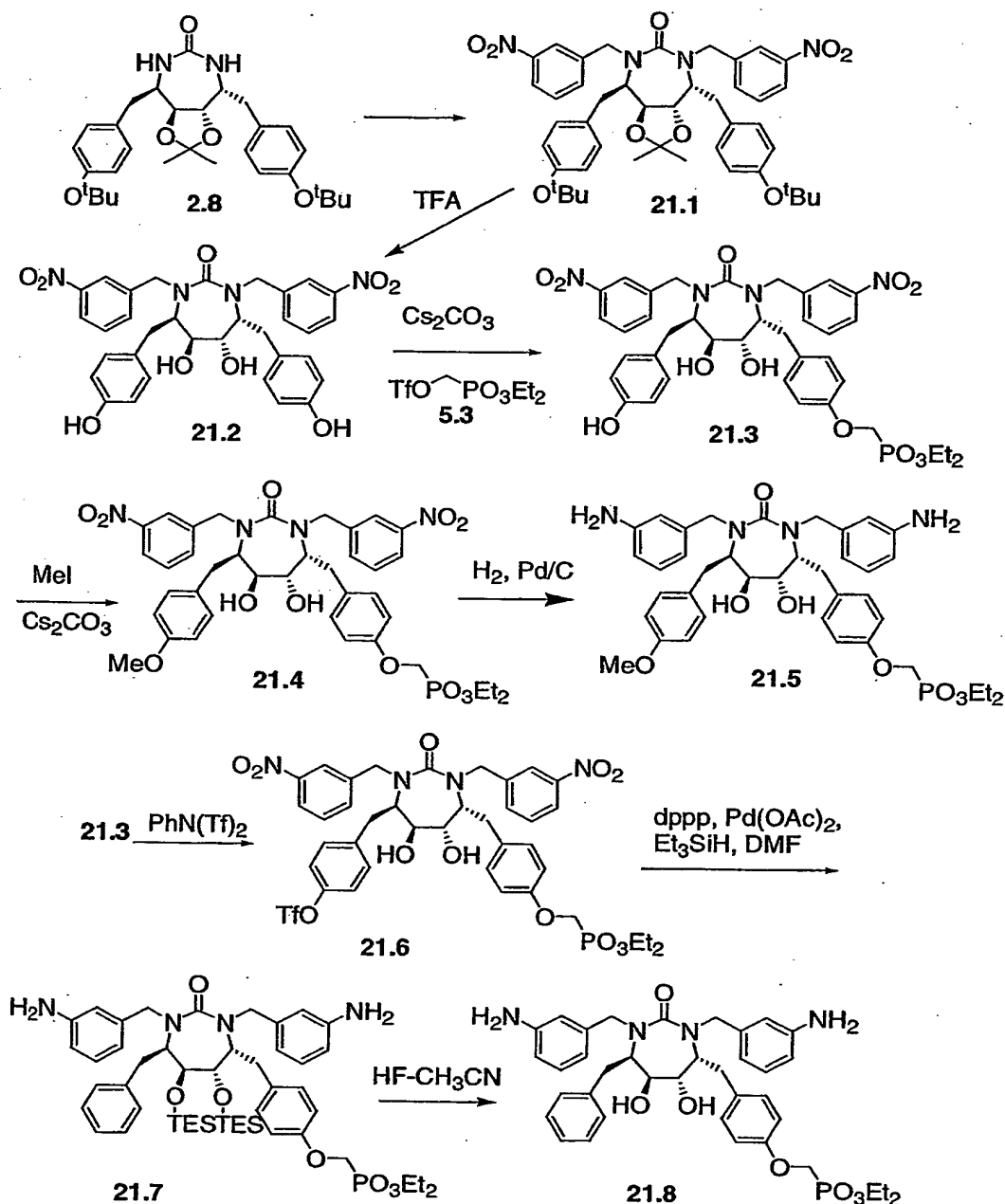
Bis-(3-nitrobenzyl) derivative 21.1: A DMF solution (2 mL) of compound **2.8** (0.3 g, 0.59 mmol) was reacted with 60%NaH (0.07 g, 1.76 mmol), 3-nitrobenzyl bromide (0.38 g, 1.76 mmol) and sodium iodide (60 mg, 0.39 mmol) at room temperature for 3 h. The reaction

mixture was partitioned between methylene chloride and saturated NaHCO₃ solution. The organic phase was isolated, dried over Na₂SO₄, concentrated under reduced pressure, and purified by silica gel chromatography to give the desired product **21.1** (0.37 g, 82%).

5   **Diphenol derivative 21.2:** A methylene chloride solution (4 mL) of **21.1** (0.37 g, 0.47 mmol) was treated with TFA (1 mL) at room temperature for 3 h, and then concentrated under reduced pressure, and azeotroped with CH₃CN twice to give diphenol derivative **21.2** (0.3 g, quantitative).

10   **Monophosphonate derivative 21.3:** A THF solution (8 mL) of **18.2** (0.28g, 0.44 mmol) was stirred with cesium carbonate (0.17 g, 0.53 mmol) and diethylphosphonate triflate **5.3** (0.14 g, 0.44 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified to give **21.3** (120 mg, 35%), and recovered **21.2** (150 mg, 53%).

15

Methoxy derivative 21.4: A THF solution (2 mL) of **21.3** (9 mg, 11 μmol) was treated with cesium carbonate (15 mg, 46 μmol) and iodomethane (10 eq. Excess) at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated NaHCO₃. The organic phase was separated, dried over 20   sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford **21.4** (9 mg)

Diethylphosphonate 21.5: A ethyl acetate/ethanol (2 mL/0.5 mL) solution of **21.4** (9 mg, 11 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C for 4 h. The catalyst was 25   removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product 21.5 (4.3 mg, 49%, 2 steps). NMR (CDCl₃ + ~10 %CD₃O): δ 7.0-7.10 (m, 6 H), 6.8-6.95 (m, 4H), 6.5-6.6 (m, 4H), 6.4-6.45 (m, 2H), 4.72 (d, 2H), 4.18-4.3 (m, 6H). 3.72 (s, 3H), 3.4-3.5 (m, 4H), 2.8-3.0 (m, 6H), 1.34 (t, 6H). P NMR (CDCl₃ + ~10 %CD₃OD): 19.93 ppm.

30

Triflate 21.6: A THF solution (6 mL) of **21.3** (0.1g, 0.14 mmol), cesium carbonate (0.07 g, 0.21 mmol), and N-phenyltrifluoromethane-sulfonimide (60mg, 0.17 mmol) was stirred at

room temperature for 4 h, and then concentrated under reduced pressure, and worked up. The residue was purified by silica gel chromatography to give **21.6** (116 mg, 90%).

Diamine 21.7: A DMF solution (2 mL) of **21.6** (116 mg, 127 μmol), dppp (60 mg, 145

5   μmol), and Pd(OAc)₂ (30 mg, 134 μmol) was stirred under nitrogen, followed by addition of triethylsilane (0.3 mL), and reacted for 4 h at room temperature. The reaction mixture was worked up and purified to give **21.7** (50 mg).

Diethyl phosphonate 21.8: An acetonitrile solution (1 mL) of crude **21.7** (50 mg) was

10   treated with 48% HF (0.1 mL) for 4 h. The reaction mixture was concentrated under reduced pressure, and purified to give **21.8** (10 mg, 11% (2 steps). NMR (CDCl₃ + ~10%CD₃O): δ 7.05-7.30 (m, 9 H), 6.8-6.95 (d, 2H), 6.4-6.6 (m, 6H), 4.72 (d, 2H), 4.18-4.3 (m, 6H). 3.4-3.5 (m, 4H), 2.8-3.0 (m, 6H), 1.34 (t, 6H). P NMR (CDCl₃ + ~10 %CD₃OD): 19.83 ppm.

15   **Scheme 22**
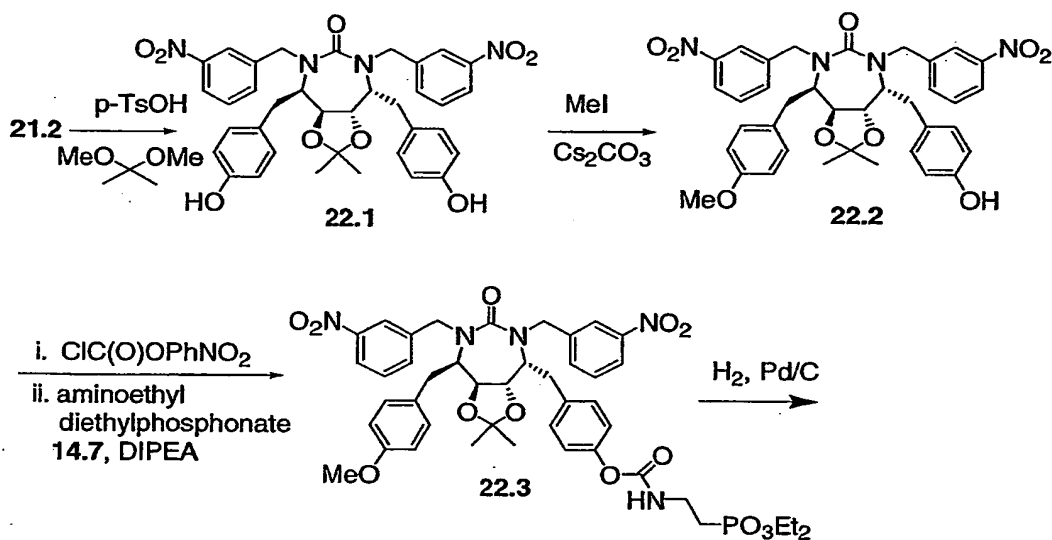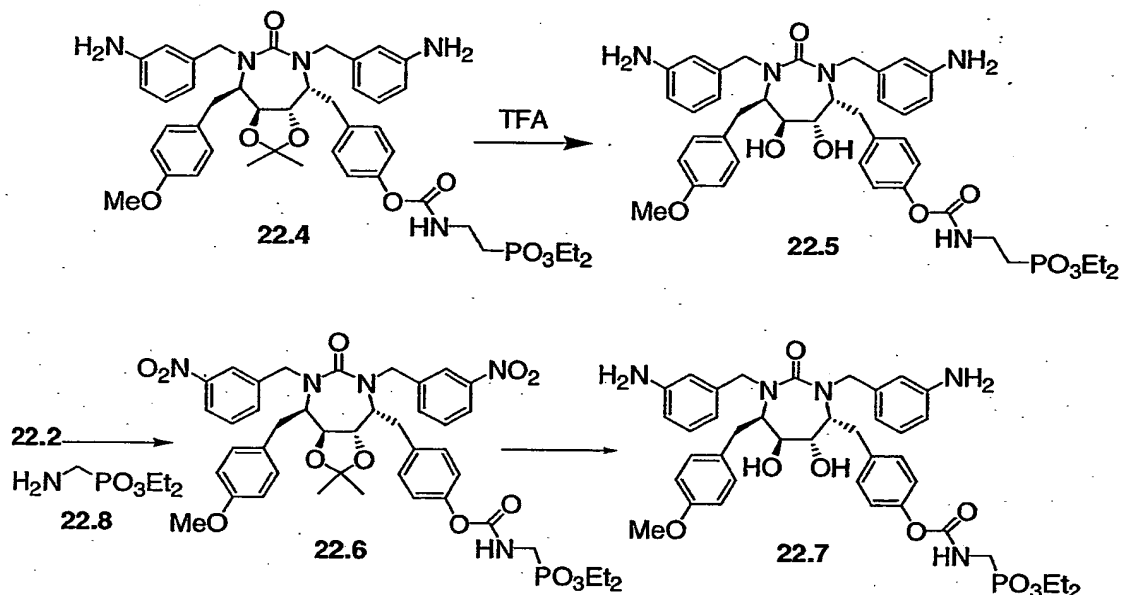
Acetonide 22.1: An acetone/2,2-diemethoxypropane solution (15 mL/5 mL) of compound 21.2 (240 mg, 0.38 mmol) and pyridinium toluenesulfonate (10 mg) was heated at reflux for 30 min. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between methylene chloride and saturated NaHCO$_3$ aqueous solution, dried, concentrated under reduced pressure and purified to afford 22.1 (225 mg, 88%).

Monomethoxy derivative 22.2: A THF solution (10 mL) of 22.1 (225 mg, 0.33 mmol) was treated with cesium carbonate (160 mg, 0.5 mmol) and iodomethane (52 mg. 0.37 mmol) at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and purified by preparative silica gel column chomatography to afford 22.2 (66 mg, 29%) and recovered starting material 22.1 (25 mg, 11%).

Diethyl phosphonate 22.3: A methylene chloride solution (2 mL) of 22.2 (22 mg, 32 µmol), DIPEA (9 mg, 66 µmol), and p-nitrophenyl chloroformate (8 mg, 40 µmol) was stirred at room temperature for 30 min. The resulting reaction mixture was reacted with DIPEA (10 mg, 77 µmol), and aminoethyl diethylphosphonate 14.7 (12 mg. 45 µmol) at room temperature overnight. The reaction mixture was washed with 5% citric acid solution, saturated NaHCO$_3$, dried, and purified by preparative TLC to afford 22.3 (12 mg, 43%).

Bis(3-aminobenzyl)-diethylphosphonate ester 22.5: An ethyl acetate/t-BuOH (4 mL/2 mL)
solution of **22.3** (12 mg, 13 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C 95
mg) at room temperature for 5 h. The catalyst was removed by filtration. The filtrate was
5   concentrated under reduced pressure, and purified by preparative TLC to give **22.4** (8 mg,
72%). A methylene chloride solution (0.5 mL) of **22.4** (8 mg) was treated with TFA (0.1
mL) at room temperature for 1 h., concentrated under reduced pressure, and then azeotroped
with CH_3CN twice to afford **22.5** (8.1 mg, 81%). NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.2 (d,
1H), 6.95-7.15 (m, 6H), 6.75-6.9 (m, 5 H), 4.66 (d, 1H), 4.46 (d, 1H), 4.06-4.15 (m, 4H). 3.75
10 (s, 3H), 3.6-3.7 (m, 4H), 2.6-3.1 (m, 6H), 2.0-2.1 (m, 2H), 1.30 (t, 6H). P NMR ($CDCl_3$ +
~10 %CD_3OD): 29.53 ppm. MS: 790 (M + 1).

Bis(3-aminobenzyl) diethylphosphonate ester 22.7: Compound **22.7** was prepared from
22.2 (22 mg, 32 μmol) and aminomethyl diethylphosphonate **22.8** as shown above for the
15 preparation of **22.5** from **22.2**. NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.24 (d, 1H), 6.8-7.12 (m,
11H), 4.66 (d, 1H), 4.45 (d, 1H), 4.06-4.15 (m, 4H). 3.75 (s, 3H), 2.6-3.1 (m, 6H), 1.30 (t,
6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 22.75 ppm. MS: 776 (M + 1).

Scheme 23
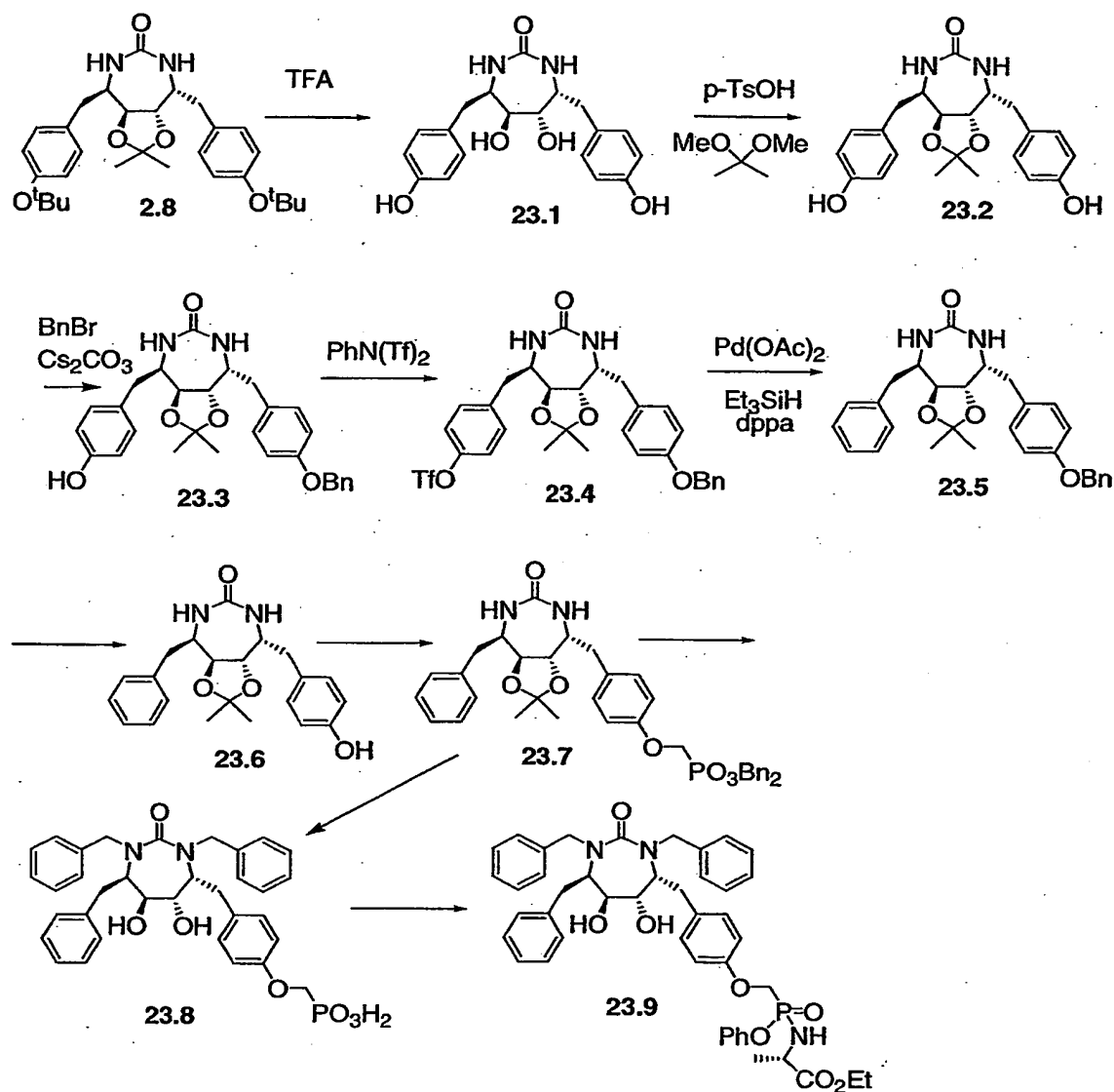
5

Diol 23.1: To a solution of compound 2.8 (2.98 g, 5.84 mmol) in methylene chloride (14 mL) was added TFA (6 mL). The resulted mixture was stirred at room temperature for 2 h. Methanol (5 mL) and additional TFA (5 mL) were added. The reaction mixture was stirred for additional 4 h and then concentrated under reduced pressure. The residue was washed

10 with hexane/ethyl acetate (1:1) and dried to afford compound 23.1 (1.8 g, 86%) as an off-white solid.

Benzyl ether 23.3: To a solution of compound **23.1** (1.8 g, 5.03 mmol) in DMF (6 mL) and 2,2-dimethoxyl propane (12 mL) was added p-toluenesulfonic acid monohydrate (0.095 g, 0.5 mmol). The resultant mixture was stirred at 65°C for 3 h. The excess 2,2-dimethoxyl propane was slowly distilled. The reaction mixture was cooled to room temperature and

5 charged with THF (50 mL), benzyl bromide (0.8 mL, 6.73 mmol) and cesium carbonate (2.0 g, 6.13 mmol). The resulted mixture was stirred at 65°C for 16 h. The reaction was quenched with acetic acid aqueous solution (4%, 100 mL) at 0°C, and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired

10 mono protected compound **23.3** (1.21 g, 49%).

Benzyl ether 23.5: To a solution of compound **23.3** (0.65 g, 1.33 mmol) and N-phenyltrifluoromethanesulfonimide (0.715 g, 2 mmol) in THF (12 mL) was added cesium carbonate (0.65 g, 2 mmol). The mixture was stirred at room temperature for 3 h. The

15 reaction mixture was filtered through a pad of silica gel and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give triflate **23.4** (0.85 g). To a solution of 1,3-bis(diphenylphosphino)propane (0.275g, 0.66 mmol) in DMF (10 mL) was added palladium(II) acetate (0.15 g, 0.66 mmol) under argon. This mixture was stirred for 2 min. and then added to triflate **23.4**. After stirring for 2 min., triethylsilane was added

20 and the resulted mixture was stirred for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to afford compound **23.5** (0.56 g, 89%).

Phenol 23.6: A solution of **23.5** (0.28 g, 0.593 mmol) in ethyl acetate (5 mL) and isopropyl

25 alcohol (5 mL) was treated with 10% Pd/C (0.05g) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield **23.6** (0.22 g, 97%) as a white solid.

Dibenzyl phosphonate 23.7: To a solution of compound **23.6** (0.215 g, 0.563 mmol) in THF

30 (10 mL) was added dibenzyl triflate **3.11** (0.315 g, 0.74 mmol) and cesium carbonate (0.325g, 1 mmol). The mixture was stirred at room temperature for 2 h, then diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, filtered and

concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **23.7** (0.31 g, 84%).

Diphenyl ester 23.8: A solution of compound **23.7** (0.3 g, 0.457 mmol) and benzyl bromide

5   (0.165 mL, 1.39 mmol) in THF (10 mL) was treated with potassium *tert*-butoxide (1M/THF, 1.2 mL) for 0.5 h. The mixture was diluted with ethyl acetate and washed with HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and treated with 10% Pd/C (0.05 g) under hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by

10   filtration and the filtrate was concentrated under reduced pressure. The residue was treated with TFA (1 mL) in methanol (5 mL) for 1 h, and then concentrated under reduced pressure. The residue was dissolved in pyridine (1 mL) and mixed with phenol (0.45 g, 4.8 mmol) and 1,3-dicyclohexylcarbodiimide (0.38 g, 1.85 mmol). The mixture was stirred at 70°C for 2 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl

15   acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound **23.8** (0.085 g, 24%).

Mono amidate 23.9: To a solution of **23.8** (0.085g, 0.11 mmol) in acetonitrile (1 mL) was

20   added sodium hydroxide (1N, 0.25 mL) at 0°C. After stirred at 0°C for 1 h, the mixture was acidified with Dowex resin to pH = 3, and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in pyridine (0.5 mL) and mixed with L-alanine ethyl ester hydrochloride (0.062 g, 0.4 mmol) and 1,3-dicyclohexyl-carbodiimide (0.125 g, 0.6 mmol). The mixture was stirred at 60°C for 0.5 h, and then concentrated under reduced

25   pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by HPLC (C-18, 65% acetonitrile / water) to afford compound **23.9** (0.02 g, 23%). ^{1}H NMR (CDCl3): δ 1.2 (m, 3H), 1.4 (m, 3H), 1.8 (brs, 2H), 2.8-3.1 (m, 6H), 3.5-3.7 (m, 4H), 3.78 (m, 1H), 4.0-4.18 (m, 2H), 4.2-4.4 (m, 3H), 4.9 (m, 2H), 6.8-7.4 (m, 24H). 31P NMR (CDCl3): d

30   20.9, 19.8. MS: 792 (M+1).

Scheme 24
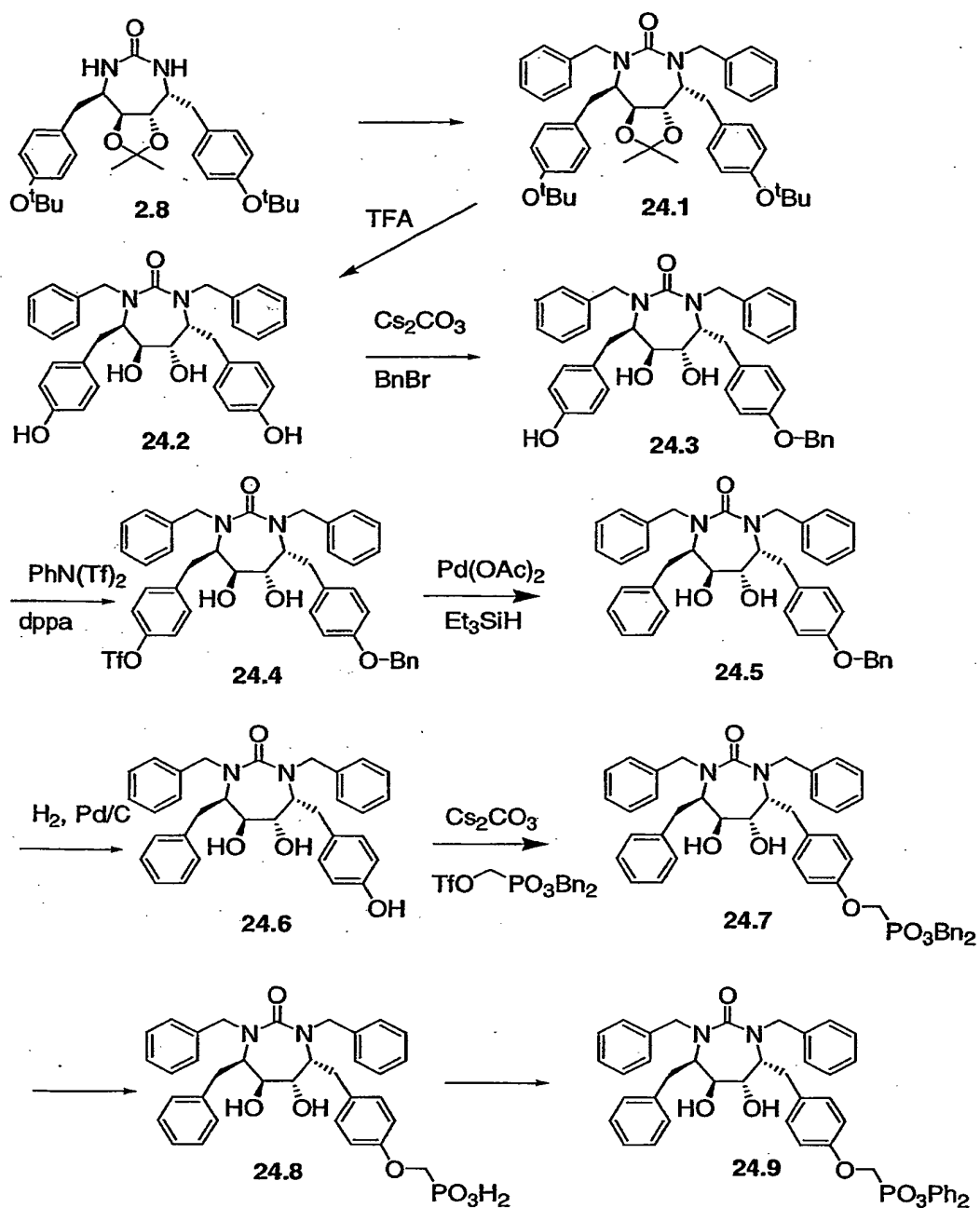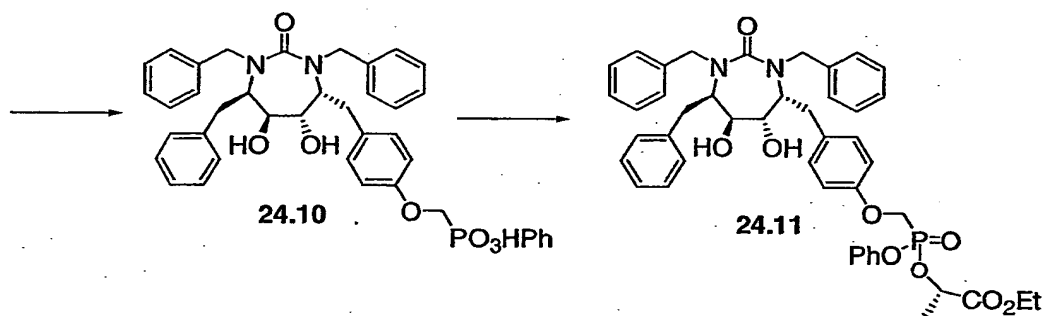
Di-tert butyl ether 24.1: To a solution of compound 2.8 (0.51 g, 1 mmol) and benzyl bromide (0.43g, 2.5 mmol) in THF (6 mL) was added potassium *tert*-butoxide (1M/THF, 2.5 mL). The mixture was stirred at room temperature for 0.5 h, then diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **24.1** (0.62 g, 90%).

Diol 24.2: To a solution of compound **24.1** (0.62 g, 0.9 mmol) in methylene chloride (4 mL) was added TFA (1 mL) and water (0.1 mL). The mixture was stirred for 2 h, and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **24.2** (0.443g, 92%).

Benzyl ether 24.3: Compound **24.3** was prepared in 46% yield according to the procedure described in Scheme 23 for the preparation of **23.3**.

Triflate 24.4: Compound **24.4** was prepared in 95% yield according to the procedure described in Scheme 23 for the preparation of **23.4**.

Benzyl ether 24.5: Compound **24.5** was prepared in 93% yield according to the procedure described in Scheme 23 for the preparation of **23.5**.

Phenol 24.6: Compound **24.6** was prepared in 96% yield according to the procedure described in Scheme 23 for the preparation of **23.6** from **23.5**.

Dibenzyl phosphonate 24.7: Compound **24.7** was prepared in 82% yield according to the

5   procedure described in Scheme 23 for the preparation of **23.7**.

Diacid 24.8: A solution of **24.7** (0.16 g, 0.207 mmol) in ethyl acetate (4 mL) and isopropyl alcohol (4 mL) was treated with 10% Pd/C (0.05g) and stirred under a hydrogen atmosphere (balloon) for 4 h. The catalyst was removed by filtration and the filtrate was concentrated

10   under reduced pressure to yield **24.8** (0.125 g, 98%) as a white solid.

Diphenyl ester 24.9: To a solution of compound **24.8** (0.12 g, 0.195 mmol) in pyridine (1 mL) was added phenol (0.19 g, 2 mmol) and 1,3-dicyclohexylcarbodiimide (0.206 g, 1 mmol). The mixture was stirred at 70°C for 2 h, and then concentrated under reduced

15   pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound **24.9** (0.038 g, 25%).

Mono lactate 24.11: Compound **24.9** was converted, via compound **24.10**, into compound

20   **24.11** in 36% yield according to the procedure described in Scheme 23 for the preparation of **23.9** except utilizing the ethyl lactate ester in place of L-alanine ethyl ester . ^{1}H NMR (CDCl3): δ 1.05 (t, J = 8 Hz, 1.5H), 1.1 (t, J = 8 Hz, 1.5H), 1.45 (d, J = 8 Hz, 1.5H), 1.55 (d, J = 8 Hz, 1.5H), 2.6 (brs, 2H), 2.9-3.1 (m, 6H), 3.5-3.65 (m, 4H), 4.15-4.25 (m, 2H), 4.4-4.62 (m, 2H), 4.9 (m, 2H), 5.2 (m, 1H), 6.9-7.4 (m, 24H). 31P NMR (CDCl3): d 17.6, 15.5. MS:

25   793 (M+1).

Scheme 25
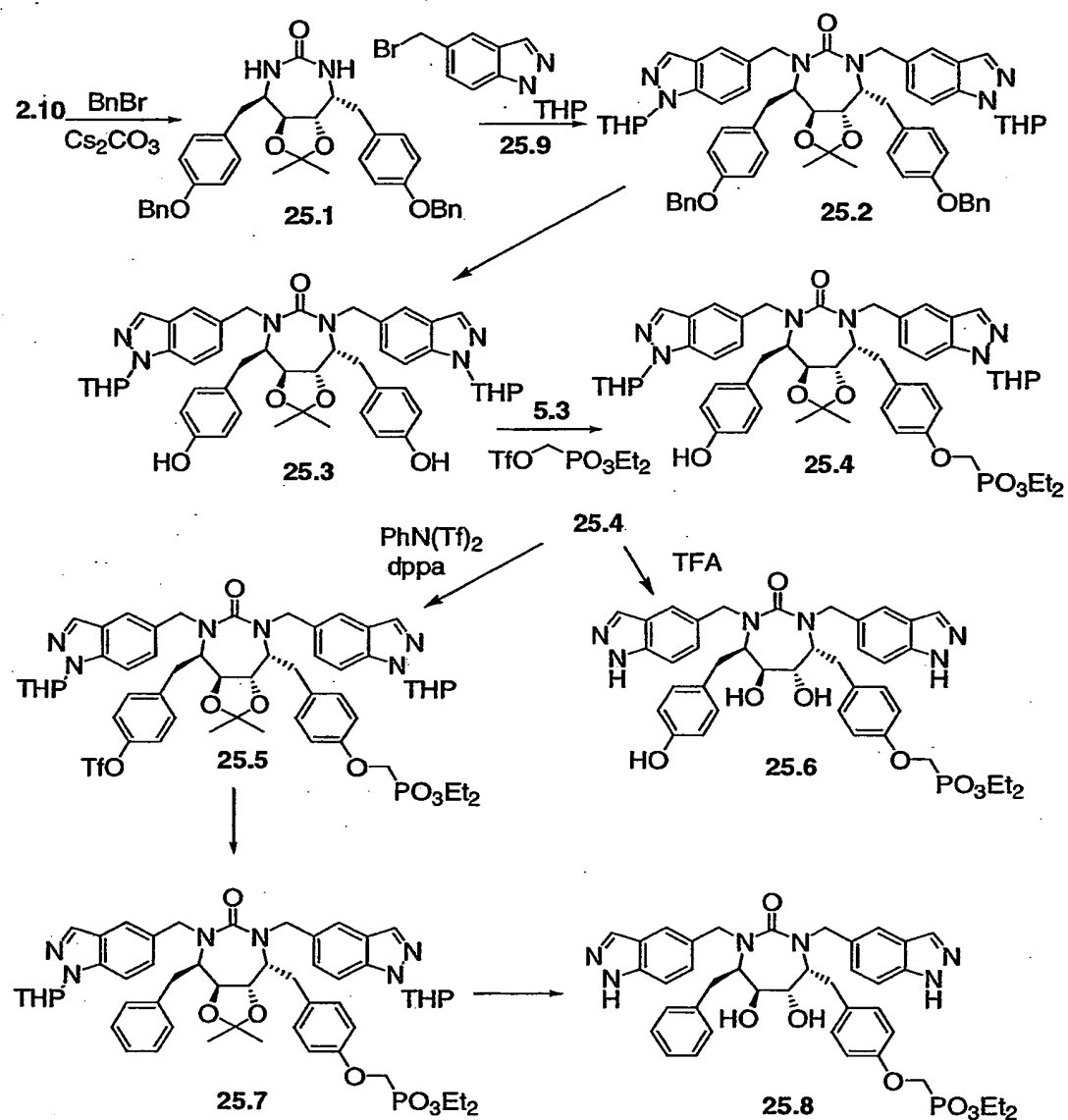
5   **Dibenzyl ether 25.1:** The protection reaction of compound **2.10** with benzyl bromide was carried out in the same manner as described in Scheme 23 to afford compound **25.1**.

Bis indazole 25.2: The alkylation of compound **25.1** with bromide **25.9** was carried out in the same manner as described in Scheme 23 to afford compound **25.2** in 96% yield.

10

Diol 25.3: A solution of 25.2 (0.18 g, 0.178 mmol) in ethyl acetate (5 mL)) and isopropyl alcohol (5 mL) was treated with 20% Pd(OH)2/C (0.09g) and stirred under a hydrogen atmosphere (balloon) for 24 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford 25.3 in quantitative yield.

5

Diethyl phosphonate 25.4: To a solution of compound 25.3 (0.124 g, 0.15 mmol) in acetonitrile (8 mL) and DMF (1 mL) was added potassium tert-butoxide (0.15 mL, 1M/THF). The mixture was stirred for 10 min. to form a clear solution. Diethyl triflate 5.3 (0.045 g, 0.15 mmol) was added to the reaction mixture. After stirred for 0.5 h, the reaction mixture

10   was diluted with ethyl acetate and washed with HCl (0.1N). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound 25.4 (0.039 g, 55% (based on recovered starting material: 0.064 g, 52%).

15   **Bisindazole 25.6:** A mixture of compound 25.4 (0.027 g), ethanol (1.5 mL), TFA (0.6 mL) and water (0.5 mL) was stirred at 60°C for 18 h. The mixture was concentrated under reduced pressure, and the residue was purified by HPLC to afford compound 25.6 as a TFA salt (0.014 g, 51%). ^{1}H NMR (CD3OD): δ 1.4 (t, J = 8 Hz, 6H), 2.9 (M, 4H), 3.2 (m, 2H), 3.58 (brs, 2H), 3.65 (m, 2H), 4.25 (m, 4H), 4.42 (d, J = 10 Hz, 2H), 4.85 (m, 2H), 6.75 (d, J =

20   9 Hz, 2H), 6.9 (m, 4H), 7.0 (d, J = 9 Hz, 2H), 7.4-7.6 (m, 6H), 8.1 (brs, 2H). 31P NMR (CD3OD): δ 20.8. MS: 769 (M+1).

Diethyl phosphonate 25.7: Compound 25.4 was converted into compound 25.7 in 76% yield according to the procedures described in Scheme 23 for the conversion of 23.3 into

25   23.5.

Bis indazole 25.8: Compound 25.7 (0.029 g) was treated in the same manner as compound 25.4 in the preparation of 25.6 to afford compound 25.8 as a TFA salt (0.0175 g, 59%). ^{1}H NMR (CD3OD): δ 1.4 (t, J = 8 Hz, 6H), 3.0 (M, 4H), 3.15 (d, J = 14 Hz, 1H), 3.25 (d, J = 14

30   Hz, 1H), 3.58 (brs, 2H), 3.65 (m, 2H), 4.25 (m, 4H), 4.42 (d, J = 10 Hz, 2H), 4.85 (m, 2H), 6.9 (d, J = 9 Hz, 2H), 7.0 (d, J = 9 Hz, 2H), 7.1 (d, J = 7 Hz, 2H), 7.2-7.6 (m, 9H), 8.1 (brs, 2H). ^{31}P NMR (CD3OD): δ 20.8. MS: 753 (M+1).

Preparation of Alkylating and Phosphonate Reagents

Scheme 50

50.1

3.9

50.2

50.3

3.11

50.4

6.9

50.5

14.5
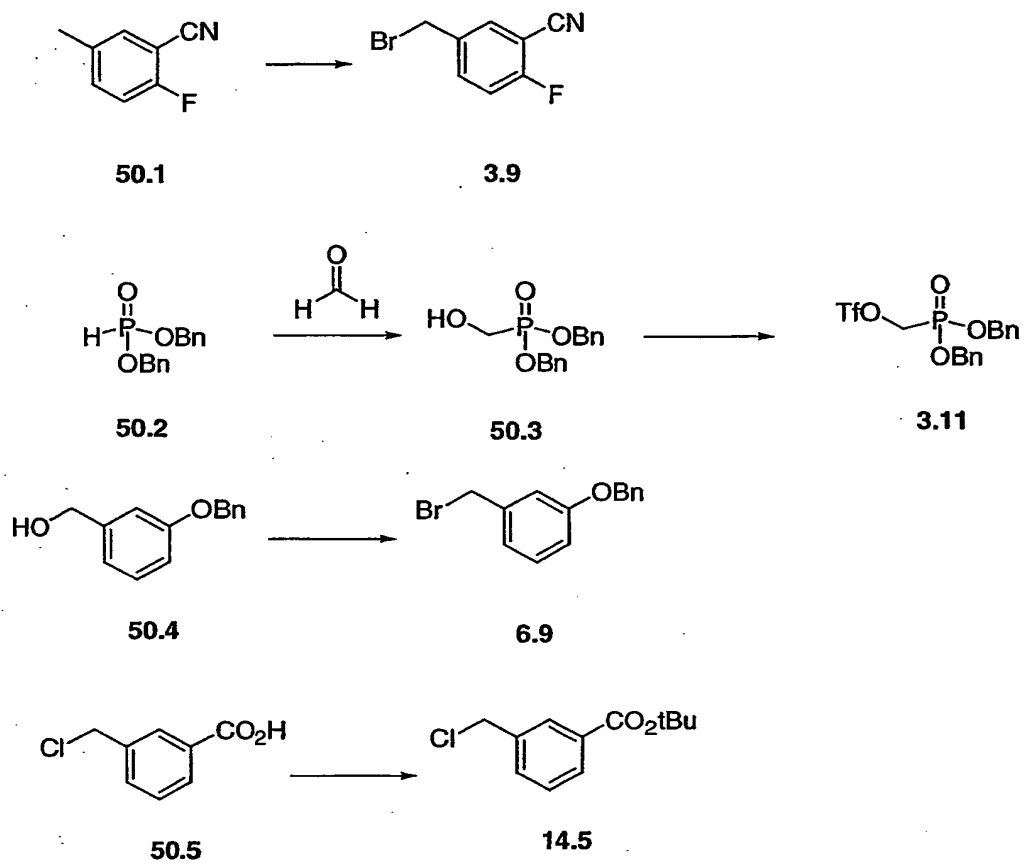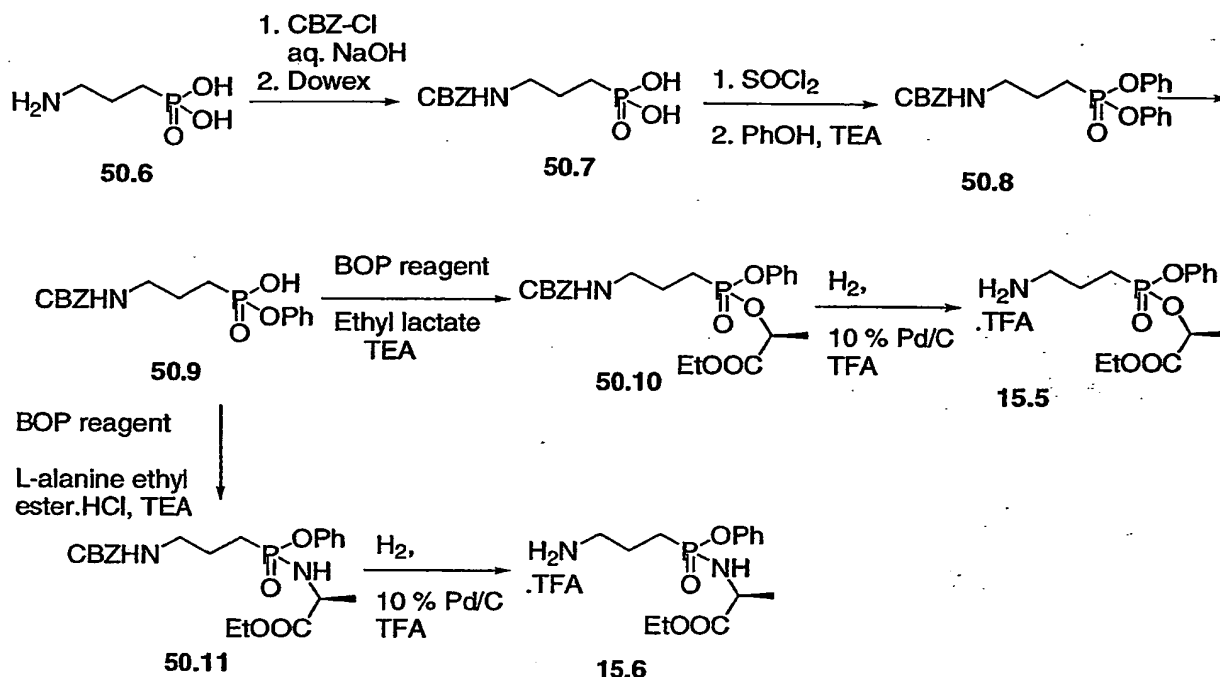
3-cyano-4-fluoro-benzylbromide 3.9: The commercially available 2—fluoro-4-methylbenzonitrile **50.1** (10 g, 74 mmol) was dissolved in carbon tetrachloride (50 mL) and

5   then treated with NBS (16 g, 90 mmol) followed by AIBN (0.6 g, 3.7 mmol). The mixture was stirred at 85°C for 30 min and then allowed to cool to room temperature. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel eluting with 5-20% ethyl acetate in hexanes to give **3.9** (8.8 g, 56%).

10   **4-benzyloxy benzyl chloride 3.10** is purchased from Aldrich

Dibenzyl triflate 3.11: To a solution of dibenzyl phosphite **50.2** (100 g, 381 mmol) and formaldehyde (37% in water, 65 mL, 860 mmol) in THF (200 mL) was added TEA (5 mL, 36 mmol). The resulted mixture was stirred for 1 h, and then concentrated under reduced

15   pressure. The residue was dissolved in methylene chloride and hexane (1:1, 300 mL), dried over sodium sulfate, filtered through a pad of silica gel (600 g) and eluted with ethyl acetate and hexane (1:1). The filtrate was concentrated under reduced pressure. The residue **50.3** (95 g) was dissolved in methylene chloride (800 mL), cooled to −78°C and then charged with pyridine (53 mL, 650 mmol). To this cooled solution was slowly added

20   trifluoromethanesulfonic anhydride (120 g, 423 mmol). The resulted reaction mixture was

stirred and gradually warmed up to –15°C over 1.5 h period of time. The reaction mixture
was cooled down to about – 50°C, diluted with hexane-ethyl acetate (2:1, 500 mL) and
quenched with aqueous phosphoric acid (1M, 100 mL) at –10°C to 0°C. The mixture diluted
with hexane-ethyl acetate (2:1, 1000 mL). The organic phase was washed with water, dried

5   over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was
purified by chromatography on silica gel to afford dibenzyl triflate **3.11** (66 g, 41%) as a
colorless oil.

Diethyl triflate 5.3 is prepared as described in Tet Lett. 1986, 27, p1477-1480

10

3-Benzyloxybenzylbromide 6.9: To a solution of triphenyl phosphine (15.7 g, 60 mmol) in
THF (150 mL) was added a solution of carbon tetrabromide (20 g, 60 mmol) in THF (50
mL). A precipitation was formed and stirred for 10 min. A solution of 3-benzyloxybenzyl
alcohol **50.4** (10 g, 46.7 mmol) was added. After stirred for 1.5 h, the reaction mixture was

15   filtered and concentrated under reduced pressure. The majority of triphenyl phosphine oxide
was removed by precipitation from ethyl acetate-hexane. The crude product was purified by
chromatography on silica gel and precipitation from hexane to give the desired product 3-
Benzyloxybenzylbromide **6.9** (10 g, 77%) as a white solid.

20   **t-Butyl-3-chloromethyl benzoate 14.5**: A benzene solution (15 ml) of 3-
chloromethylbenzoic acid **50.5** (1 g, 5.8 mmol) was heated at reflux, followed by the slow
addition of N,N-dimethylforamide-di-t-butylacetal (5 m). The resulting solution was refluxed
for 4 h, concentrated under reduced pressure and purified by silica gel column to afford **14.5**
(0.8 g, 60 %).

25

Aminopropyl-diethylphosphonate 14.6 is purchased from Acros

Aminoethyl-diethylphosphonate oxalate 14.7 is purchased from Acros

30   **Aminopropyl-phenol-ethyl lactate phosphonate 15.5**

N-CBZ-aminopropyl diphenylphosphonate 50.8: An aqueous sodium hydroxide solution
(50 mL of 1 N solution, 50 mmol) of 3-aminopropyl phosphonic acid **50.6** (3 g, 1.5 mmol)

-1582-

was reacted with CBZ-Cl (4.1 g, 24 mmol) at room temperature overnight. The reaction
mixture was washed with methylene chloride, acidified with Dowex 50wx8-200. The resin
was filtered off. The filtrate was concentrated to dryness. The crude N-CBZ-aminopropyl
phosphonic acid 50.7 (5.8 mmol) was suspended in CH_3CN (40 mL), and reacted with

5   thionyl chloride (5.2 g, 44 mmol) at reflux for 4 hr, concentrated, and azeotroped with
CH_3CN twice. The reaction mixture was redissolved in methylene chloride (20 mL),
followed by the addition of phenol (3.2 g, 23 mmol), was cooled to 0°C. To this 0°C cold
solution was added TEA (2.3 g, 23 mmol), and stirred at room temperature overnight. The
reaction mixture was concentrated and purified on silica gel column chromatograph to afford

10   50.8 (1.5 g, 62 %).

Monophenol derivative 50.9: A CH_3CN solution (5 mL) of 50.8 (0.8 g, 1.88 mmol) was
cooled to 0°C , and treated with 1N NaOH aqueous solution (4 mL, 4 mmol) for 2 h. The
reaction was diluted with water, extracted with ethyl acetate, acidified with Dowex 50wx8-

15   200. The aqueous solution was concentrated to dryness to afford 50.9 (0.56 g, 86%).

Monolactate derivative 50.10: A DMF solution (1 mL) of crude 50.9 (0.17 g, 0.48 mmol),
BOP reagent (0.43 g, 0.97 mmol), ethyl lactate (0.12 g, 1 mmol), and DIPEA (0.31 g, 2.4
mmol) was reacted for 4 hr at room temperature. The reaction mixture was partitioned

20   between methylene chloride and 5 % citric acid aqueous solution. The organic solution was
separated, concentrated, and purified on preparative TLC to give 50.10 (0.14 g, 66%).

3-Aminopropyl lactate phosphonate 15.5: An ethyl acetate/ethanol solution (10 mL/2 mL)
of 50.10 (0.14 g, 0.31 mmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (40

25   mg) for 3 hr. The catalyst was filtered off. The filtrate was concentrated to dryness to afford
15.5 (0.14 g, quantitative). NMR ($CDCl_3$): δ 8.0-8.2 (b, 3H), 7.1-7.4 (m, 5H), 4.9-5.0 (m,
1H), 4.15-4.3 (m, 2H), 3.1-3.35 (m, 2H), 2.1-2.4 (m, 4H), 1.4 (d, 3H), 1.3 (t, 3H).

Aminopropyl-phenol-ethyl alanine phosphonate 15.6: Compound 15.6 (80 mg) was

30   prepared from the reaction of 50.9 (160 mg, 0.45 mmol) and L-alanine ethyl ester
hydrochloride salt (0.11g, 0.68 mmol) in the presence of DIPEA and BOP reagent to give
50.11, followed by the hydrogenation in the presence of 10% Pd/C and TFA to yield 15.6.
NMR ($CDCl_3$ + ~10 % CD_3OD): δ 8.0-8.2 (b), 7.25-7.35 (t, 2H), 7.1-7.2 (m, 3H), 4.0-4.15

(m, 2H), 3.8-4.0 (m, 1H), 3.0-3.1 (m, 2H), 1.15-1.25 (m, 6H). P NMR (CDCl₃ + ~10 %
CD₃OD): 32.1 & 32.4 ppm.

Aminopropyl dibenzyl phosphonate 15.7 :

N-BOC-3-aminopropyl phosphonic acid 50.13: A THF-1N aqueous solution (16 mL-16
mL) of 3-aminopropyl phosphonic acid **50.12** (1 g, 7.2 mmol) was reacted with (BOC)₂O (1.7
g, 7.9 mmol) overnight at room temperature. The reaction mixture was concentrated, and
partitioned between methylene chloride and water. The aqueous solution was acidified with
Dowex 50wx8-200. The resin was filtered off. The filtrate was concentrated to give **50.13**
(2.2 g, 92 %).

N-BOC-3-aminopropyl dibenzyl phosphonate 50.14: A CH₃CN solution (10 mL) of **50.13**
(0.15 g, 0.63 mmol), cesium carbonate (0.61 g, 1.88 mmol), and benzyl bromide (0.24 g, 1.57
mmol) was heated at reflux overnight. The reaction mixture was cooled to room temperature,
and diluted with methylene chloride. The white solid was filtered off, washed thoroughly
with methylene chloride. The organic phase was concentrated, and purified on preparative
TLC to give **50.14** (0.18 g, 70%). MS: 442 (M + Na).

Aminopropyl dibenzyl phosphonate 15.7: A methylene chloride solution (1.6 mL) of **50.14**
(0.18 g) was treated with TFA (0.4 mL) for 1 hr. The reaction mixture was concentrated to
dryness, and azeotroped with CH₃CN twice to afford **15.7** (0.2 g, as TFA salt). NMR
(CDCl₃): δ 8.6 (b, 2H), 7.9 (b, 2H), 7.2-7.4 (m, 10H), 4.71-5.0 (2 abq, 4H), 3.0 (b, 2H), 1.8-2
(m, 4H). 31P NMR (CDCl₃): 32.0 ppm. F NMR (CDCl₃): -76.5 ppm.

Aminomethyl diethylphosphonate 22.8 is purchased from Acros

Bromomethyl, tetrahydropyran indazole 25.9 is prepared according to J. Org. Chem. 1997,
62, p5627

Activity of the CCPPI Compounds

The enzyme inhibitory potency (Ki), antiviral activity (EC50), and cytotoxicity (CC50) of the
tested compounds were measured and demonstrated.

<u>Biological assays used for the characterization of PI prodrugs</u>

<u>HIV-1 Protease Enzyme Assay (Ki)</u>

The assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage

5   by HIV-1 protease in a defined reaction buffer as initially described by M.V.Toth and

G.R.Marshall, Int. J. Peptide Protein Res. 36, 544 (1990)

Substrate: (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg

Substrate supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-2992)

10

Enzyme: recombinant HIV-1 protease expressed in E.Coli

Enzyme supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-9040)

Reaction buffer: 100 mM ammonium acetate, pH 5.3

15   1 M sodium chloride

1 mM ethylendiaminetetraacetic acid

1 mM dithiothreitol

10% dimethylsulfoxide

20   *Assay protocol for the determination of inhibition constant Ki:*

1. Prepare series of solutions containing identical amount of the enzyme (1 to 2.5 nM) and a

tested inhibitor at different concentrations in the reaction buffer

2. Transfer the solutions (190 uL each) into a white 96-well plate

3. Preincubate for 15 min at 37°C

25   4. Solubilize the substrate in 100% dimethylsulfoxide at a concentration of 800 μM. Start

the reaction by adding 10 μL of 800 μM substrate into each well (final substrate

concentration of 40 μM)

5. Measure the real-time reaction kinetics at 37°C by using Gemini 96-well plate fluorimeter

(Molecular Devices, Sunnyvale, CA) at λ(Ex) = 330 nm and λ(Em) = 420 nm

30   6. Determine initial velocities of the reactions with different inhibitor concentrations and

calculate Ki (in picomolar concentration units) value by using EnzFitter program

(Biosoft, Cambridge, U.K.) according to an algorithm for tight-binding competitive inhibition described by Ermolieff J., Lin X., and Tang J., Biochemistry 36, 12364 (1997)

Anti-HIV-1 Cell Culture Assay (EC_{50})

The assay is based on quantification of the HIV-1-associated cytopathic effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. The HIV-1-induced cell death is determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989).

Assay protocol for determination of EC_{50}:

1. Maintain MT2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Infect the cells with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37°C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01.
3. Prepare a set of solutions containing various concentrations of the tested inhibitor by making 5-fold serial dilutions in 96-well plate (100 μL/well). Distribute the infected cells into the 96-well plate (20,000 cells in 100 μL/well). Include samples with untreated infected and untreated mock-infected control cells.
4. Incubate the cells for 5 days at 37°C.
5. Prepare XTT solution (6 mL per assay plate) at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in water-bath for 5 min at 55°C. Add 50 μL of N-methylphenazonium methasulfate (5 μg/mL) per 6 mL of XTT solution.
6. Remove 100 μL media from each well on the assay plate.
7. Add 100 μL of the XTT substrate solution per well and incubate at 37°C for 45 to 60 min in a CO_2 incubator.
8. Add 20 μL of 2% Triton X-100 per well to inactivate the virus.
9. Read the absorbance at 450 nm with subtracting off the background absorbance at 650 nm.

10. Plot the percentage absorbance relative to untreated control and estimate the EC_{50} value as drug concentration resulting in a 50% protection of the infected cells.

Cytotoxicity Cell Culture Assay (CC_{50}):

5   The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989).

10   *Assay protocol for determination of CC_{50}:*

1.   Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.

2.   Prepare a set of solutions containing various concentrations of the tested inhibitor by making 5-fold serial dilutions in 96-well plate (100 µL /well). Distribute cells into the

15   96-well plate (20,000 cells in 100 µL/well). Include samples with untreated cells as a control.

3.   Incubate the cells for 5 days at 37°C.

4.   Prepare XTT solution (6 mL per assay plate) in dark at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min.

20   Add 50 µL of N-methylphenazonium methasulfate (5 µg/mL) per 6 mL of XTT solution.

5.   Remove 100 µL media from each well on the assay plate and add 100 µL of the XTT substrate solution per well. Incubate at 37°C for 45 to 60 min in a CO_2 incubator.

6.   Add 20 µL of 2% Triton X-100 per well to stop the metabolic conversion of XTT.

7.   Read the absorbance at 450 nm with subtracting off the background at 650 nm.

25   8.   Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

30   Resistance Evaluation (*I50V and I84V/L90M fold change*)

The assay is based on the determination of a difference in the susceptibility to a particular HIV protease inhibitor between the wild-type HIV-1 strain and a mutant HIV-1 strain

-1587-

containing specific drug resistance-associated mutation(s) in the viral protease gene. The absolute susceptibility of each virus (EC_{50}) to a particular tested compound is measured by using the XTT-based cytopathic assay as described above. The degree of resistance to a tested compound is calculated as fold difference in EC_{50} between the wild type and a specific

5   mutant virus. This represents a standard approach for HIV drug resistance evaluation as documented in various publications (e.g. Maguire et al., Antimicrob. Agents Chemother. 46: 731, 2002; Gong et al., Antimicrob. Agents Chemother. 44: 2319, 2000; Vandamme and De Clercq, in Antiviral Therapy (Ed. E. De Clercq), pp. 243, ASM Press, Washington, DC, 2001).

10

HIV-1 strains used for the resistance evaluation:
Two strains of mutant viruses containing I50V mutation in the protease gene have been used in the resistance assays: one with M46I/I47V/I50V mutations (designated I50V #1) and the other with L10I/M46I/I50V (designated I50V #2) mutations in the viral protease gene. A

15   third virus with I84V/L90M mutations was also employed in the resistance assays. Mutants I50V #1 and I84V/L90M were constructed by a homologous recombination between three overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with the protease and reverse transcriptase genes deleted, 2. DNA fragment generated by PCR amplification containing reverse transcriptase gene from HXB2D strain

20   (wild-type), 3. DNA fragment of mutated viral protease gene that has been generated by PCR amplification. An approach similar to that described by Shi and Mellors in Antimicrob. Agents Chemother. 41: 2781-85, 1997 was used for the construction of mutant viruses from the generated DNA fragments. Mixture of DNA fragments was delivered into Sup-T1 cells by using a standard electroporation technique. The cells were cultured in RPMI-1640

25   medium supplemented with 10% fetal bovine serum and antibiotics until the recombinant virus emerged (usually 10 to 15 days following the electroporation). Cell culture supernatant containing the recombinant virus was harvested and stored in aliquots. After verification of protease gene sequence and determination of the infectious virus titer, the viral stock was used for drug resistance studies. Mutant I50V #2 is an amprenavir-resistant HIV-1 strain

30   selected *in vitro* from the wild-type IIIB strain in the presence of increasing concentration of amprenavir over a period of > 9 months using an approach similar to that described by Partaledis et al., J. Virol. 69: 5228-5235, 1995. Virus capable of growing in the presence of 5

μM amprenavir was harvested from the supernatant of infected cells and used for resistance assays following the titration and protease gene sequencing.

Example 37: Activity of the Tested Compounds

5   The enzyme inhibitory potency (Ki), antiviral activity (EC50), and cytotoxicity (CC50) of the tested compounds are summarized in Table 1.
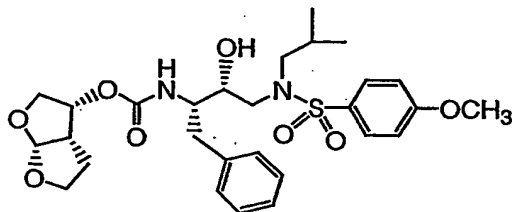
94-003

Table 1: Enzyme inhibition activity (Ki), antiviral cell culture activity (EC50), and cytotoxicity (CC50) of the tested compounds.

Substitution of (P1)phenyl	Compound	Phosphonate substitution	HIV-1 protease inhibition Ki [pM]	Anti-HIV-1 Cell Culture Activity EC50 [nM]	Cytotoxicity CC50 [μM]
none	Amprenavir	none	45.6 ± 18.2	16 ± 2.2	
none	94-003	none	1.46 ± 0.58	1.4 ± 0.3	
phosphonyl	27	diacid	11.8 ± 6.0	> 100,000	> 100
	28	diethyl	1.2 ± 0.8	5.0 ± 2.8	70
phosphonyl methoxy	11	diacid	2.1 ± 0.2	4,800 ± 1,800	> 100
	13	diethyl	2.6 ± 1.5	3.0 ± 0	50
	14	dibenzyl	12.7 ± 1.9	2.3 ± 0.4	35
	16c	bis(Ala-ethylester)	15.4 ± 0.85	105 ± 43	60
	16d	bis(Ala-butylester)	18.75 ± 3.04	6.0 ± 1.4	
	16e	bis(ABA-ethylester)	8.8 ± 1.7	12.5 ± 3.5	
	16f	bis(ABA-butylester)	3.5 ± 1.4	4.8 ± 1.8	
	16a	bis(Gly-ethylester)	29 ± 8.2	330 ± 230	
	16b	bis(Gly-butylester)	4.9 ± 1.8	17.5 ± 10.5	
	16g	bis(Leu-ethylester)	29 ± 9	6.8 ± 0.4	
	16h	bis(Leu-butylester)	31.7 ± 19.3	120 ± 42	
	16i	bis(Phe-ethylester)		17 ± 12	
	16j	bis(Phe-butylester)		35 ± 7	
	15	bis(POC)	36	825 ± 106	
	11	Monoethyl, monoacid	0.45 ± 0.15	700 ± 0	

5 Cross-Resistance Profile Assay

The assay is based on the determination of a difference in the susceptibility to a particular HIV protease inhibitor between the wild-type HIV-1 strain and a recombinant HIV-1 strain expressing specific drug resistance-associated mutation(s) in the viral protease gene. The absolute susceptibility of each virus to a particular tested compound is measured by using the

10 XTT-based cytopathic assay as described in Example B. The degree of resistance to a tested compound is calculated as fold difference in EC50 between the wild type and a specific mutant virus.

Recombinant HIV-1 strains with resistance mutations in the protease gene:

One mutant virus (82T/84V) was obtained from NIH AIDS Research and Reference Reagent
Program (Rockville, MD). Majority of the mutant HIV-1 strains were constructed by a
homologous recombination between three overlapping DNA fragments: 1. linearized plasmid
5   containing wild-type HIV-1 proviral DNA (strain HXB2D) with the protease and reverse
transcriptase genes deleted, 2. DNA fragment generated by PCR amplification containing
reverse transcriptase gene from HXB2D strain (wild-type), 3. DNA fragment generated by
RT-PCR amplification from patients plasma samples containing viral protease gene with
specific mutations selected during antiretroviral therapy with various protease inhibitors.
10   Additional mutant HIV-1 strains were constructed by a modified procedure relying on a
homologous recombination of only two overlapping DNA fragments: 1. linearized plasmid
containing wild-type HIV-1 proviral DNA (strain HXB2D) with only the protease gene
deleted, and 2. DNA fragment generated by RT-PCR amplification from patients plasma
samples containing viral protease gene with specific mutations. In both cases, mixture of
15   DNA fragments was delivered into Sup-T1 cells by using a standard electroporation
technique. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal
bovine serum and antibiotics until the recombinant virus emerged (usually 10 to 15 days
following the electroporation). Cell culture supernatant containing the recombinant virus was
harvested and stored in aliquots. After determination of the virus titer the virus stock was
20   used for drug resistance studies.

Example 39: Cross-Resistance Profile of the Tested Compounds

Cross-resistance profile of currently used HIV-1 protease inhibitors was compared with that
of the newly invented compounds (Table 2).

Table 2. Cross-resistance profile of HIV-1 protease inhibitors

Compound	EC50 [nM] WT HIV-1	8K^a 46I 90M	46I 84A	10I 48V 54V 82A	46I 47V 50V	10R 46I 82T 84V	30N 50S 82I 88D	54V 71V 82S	10F 46I 71V 82T 90M	10I 48V 71V 82A 90M	48V 54V 71V 82S	10I 84V 71V 73S 90M	Total No. of Resistant Viruses^b
Amprenavir	20	1.25	14	2	38	4	0.8	4	13	2.5	2	10	4
Nelfinavir	14	13	11	11.5	2	3	43	12	33	27	12	65	9
Indinavir	15	4	10	15	nd	7	1	10	13	28	23	43	8
Ritonavir	15	34	18	20	13	47	2	20	32	22	>50	42	10
Saquinavir	4	1	2.5	11	1	2.5	1	3	2.5	12	45	40	4
Lopinavir	8	nd	9	nd	19	11	nd	nd	7.5	4.5	60	11	6
Tipranavir	80	nd	1	0.4	0.5	5	0.5	3.5	3	0.3	2	nd	1
94-003	0.5	nd	8	0.5	29	nd	0.4	3.5	nd	nd	nd	8	3
GS 16503	16	1.2	1	0.4	3.3	1	0.6	0.9	1	0.4	0.5	2	0
GS 16571	22	1.8	1	0.3	0.8	0.6	0.7	0.6	0.8	0.2	0.2	0.9	0
GS 16587	15	1.5	1	0.5	2	1	1	0.9	1	0.4	0.4	1	0

[a] Resistance-associated mutations present in the viral protease. The highlighted changes represent primary resistance mutations.

[b] Resistance is considered as a 5-fold and higher change in the EC50 value of the mutant virus relative to the wild-type virus.

Example Section N

Plasma and PBMC Exposure Following Intravenous and Oral Administration of Prodrug to
5   **Beagle Dogs**

The pharmacokinetics of a phosphonate prodrug GS77366 (P1-monoLac-iPr), its active

metabolite (metabolite X, or GS77568), and GS8373 were studied in dogs following

intravenous and oral administration of the prodrug.

10

Dose Administration and Sample Collection. The in-life phase of this study was conducted

in accordance with the USDA Animal Welfare Act and the Public Health Service Policy on

Humane Care and Use of Laboratory Animals, and followed the standards for animal

husbandry and care found in the Guide for the Care and Use of Laboratory Animals, 7th

15   Edition, Revised 1996. All animal housing and study procedures involving live animals were

carried out at a facility which had been accredited by the Association for Assessment and

Accreditation of Laboratory Animal Care - International (AAALAC).

Each animal in a group of 4 female beagle dogs was given a bolus dose of GS77366 (P1-

20   monoLac-iPr) intravenously at 1 mg/kg in a formulation containing 40% PEG 300, 20%

propylene glycol and 40% of 5% dextrose. Another group of 4 female beagle dogs was

dosed with GS77366 via oral gavage at 20 mg/kg in a formulation containing 60% Vitamin-E

TPGS, 30% PEG 400 and 10% propylene glycol.

25   Blood samples were collected pre-dose, and at 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12

hr and 24 hr post-dose. Plasma (0.5 to 1 mL) was prepared from each sample and kept at -

70°C until analysis. Blood samples (8 mL) were also collected from each dog at 2, 8 and 24

hr post dose in Becton-Dickinson CPT vacutainer tubes. PBMCs were isolated from the

blood by centrifugation for 15 minutes at 1500 to 1800 G. After centrifugation, the fraction

30   containing PBMCs was transferred to a 15 mL conical centrifuge tube and the PBMCs were

washed twice with phosphate buffered saline (PBS) without Ca^{2+} and Mg^{2+}. The final wash

of the cell pellet was kept at -70°C until analysis.

Measurement of the prodrug, metabolite X and GS8373 in plasma and PBMCs. For plasma

35   sample analysis, the samples were processed by a solid phase extraction (SPE) procedure

outlined below. Speedisk C18 solid phase extraction cartridges (1 mL, 20 mg, 10 µM, from

J.T. Baker) were conditioned with 200 µL of methanol followed by 200 µL of water. An

aliquot of 200 µL of plasma sample was applied to each cartridge, followed by two washing

steps each with 200 µL of deionized water. The compounds were eluted from the cartridges

with a two-step process each with 125 µL of methanol. Each well was added 50 µL of water

5   and mixed. An aliquot of 25 µL of the mixture was injected onto a ThermoFinnigan TSQ

Quantum LC/MS/MS system.

The column used in liquid chromatography was HyPURITY® C18 (50 x 2.1 mm, 3.5 um)

from Thermo-Hypersil. Mobile phase A contained 10% acetonitrile in 10 mM ammonium

10   formate, pH 3.0. Mobile phase B contained 90% acetonitrile in 10 mM ammonium formate,

pH 4.6. The chromatography was carried out at a flow rate of 250 µL/min under an isocratic

condition of 40% mobile phase A and 60% mobile phase B. Selected reaction monitoring

(SRM) were used to measure GS77366, GS8373 and Metabolite X with the positive

ionization mode on the electrospray probe. The limit of quantitation (LOQ) was 1 nM for

15   GS77366, GS8373 and GS77568 (Metabolite X) in plasma.

For PBMC sample analysis, phosphate buffered saline (PBS) was added to each PBMC pellet

to bring the total sample volume to 500 µL in each sample. An aliquot of 150 µL from each

PBMC sample was mixed with an equal volume of methanol, followed by the addition of 700

µL of 1% formic acid in water. The resulting mixture was applied to a Speedisk C18 solid

20   phase extraction cartridge (1 mL, 20 mg, 10 um, from J.T. Baker) which had been

conditioned as described above. The compounds were eluted with methanol after washing

the cartridge 3 times with 10% methanol. The solvent was evaporated under a stream of N_2,

and the sample was reconstituted in 150 µL of 30% methanol. An aliquot of 75 µL of the

solution was injected for LC/MS/MS analysis. The limit of quantitation was 0.1 ng/mL in the

25   PBMC suspension.

Pharmacokinetic Calculations. The pharmacokinetic parameters were calculated using

WinNonlin. Noncompartmental analysis was used for all pharmacokinetic calculation. The

intracellular concentrations in PBMCs were calculated from the measured concentrations in

30   PBMC suspension on the basis of a reported volume of 0.2 picoliter/cell (B.L. Robins, R.V.

Srinivas, C.Kim, N.Bischofberger, and A.Fridland, (1998) Antimicrob. Agents Chemother.

42, 612).

<u>Plasma and PBMC Concentration-time Profiles.</u>

The concentration-time profiles of GS77366, GS77568 and GS8373 in plasma and PBMCs following intravenous dosing of GS77366 were compared at 1 mg/kg in dogs. The data demonstrate that the prodrug can effectively deliver the active components (metabolite X and

5   GS8373) into cells that are primarily responsible for HIV replication, and that the active components in these cells had much longer half-life than in plasma.

The pharmacokinetic properties of GS77568 in PBMCs following oral administration of GS77366 in dogs are compared with that of nelfinavir and amprenavir, two marketed HIV protease inhibitors (Table 3). These data show that the active component (GS77568) from

10   the phosphonate prodrug had sustained levels in PBMCs compared to nelfinavir and amprenavir.

Table 3. Comparison of GS77568 with nelfinavir and amprenavir in PBMCs following oral administration in beagle dogs.

Compound	Dose	$t_{1/2}$ (hr)	$AUC_{(2-24\ hr)}$
Nelfinavir	17.5 mg/kg	3.0 hr	33,000 nM·hr
Amprenavir	20 mg/kg	1.7 hr	102,000 nM·hr
GS77568	20 mg/kg of GS77366	> 20 hr	42,200 nM·hr

Example Section O

Intracellular Metabolism/In Vitro Stability

5   1. Uptake and Persistence in MT2 cells, quiescent and stimulated PBMC

The protease inhibitor (PI) phosphonate prodrugs undergo rapid cell uptake and metabolism to produce acid metabolites including the parent phosphonic acid. Due to the presence of charges, the acid metabolites are significantly more persistent in the cells than non-charged PI's. In order to estimate the relative intracellular levels of the different PI prodrugs, three

10   compounds representative of three classes of phosphonate PI prodrugs – bisamidate phosphonate, monoamidate phenoxy phosphonate and monolactate phenoxy phosphonate (Figure 1) were incubated at 10 μM for 1 hr with MT-2 cells, stimulated and quiescent peripheral blood mononuclear cells (PBMC) (pulse phase). After incubation, the cells were washed, resuspended in the cell culture media and incubated for 24 hr (chase phase). At

15   specific time points, the cells were washed, lysed and the lysates were analyzed by HPLC with UV detection. Typically, the cell lysates were centrifuged and 100 uL of the supernatant were mixed with 200 μL of 7.5 uM amprenavir (Internal Standard) in 80% acetonitrile/20% water and injected into an HPLC system (70 μL).

20   HPLC Conditions:

Analytical Column: Prodigy ODS-3, 75 x 4.6, 3u + C18 guard at 40°C

Gradient:

Mobile Phase A: 20 mM ammonium acetate in 10% ACN/90% H$_2$O

Mobile Phase B: 20 mM ammonium acetate in 70% ACN/30% H$_2$O

25   30-100%B in 4 min, 100%B for 2 min, 30%B for 2 min at 2.5 mL/min.

Run Time: 8 min

UV Detection at 245 nm

Concentrations of Intracellular metabolites were calculated based on cell volume 0.2 μL/mLn

30   cells for PBMC and 0.338 μL / mLn (0.676 uL / mL) for MT-2 cells.

Chemical Structures of Selected Protease Inhibitor Phosphonate Prodrugs and Intracellular Metabolites:
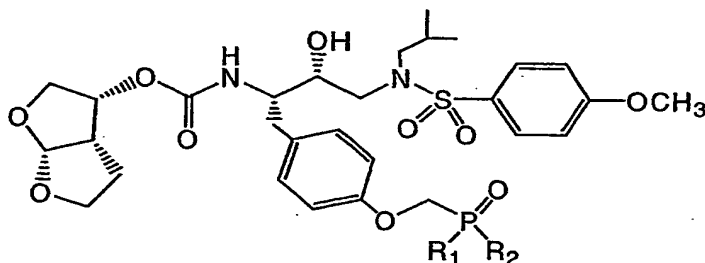
Table 4:

GS No.	R1	R2	EC_{50} (nM)
8373	OH	OH	4,800±1,800
16503	HNCH(CH₃)COOBu	HNCH(CH₃)COOBu	6.0±1.4
16571	OPh	HNCH(CH₃)COOEt	15±5
17394	OPh	OCH(CH₃)COOEt	20±7
16576	OPh	HNCH(CH₂CH₃)COOEt	12.6±4.8
Met X	OH	HNCH(CH₃)COOH	>10,000
Met LX	OH	OCH(CH₃)COOEt	1750±354

5   A significant uptake and conversion of all 3 compounds in all cell types was observed (Table
4). The uptake in the quiescent PBMC was 2-3-fold greater than in the stimulated cells. GS-
16503 and GS-16571 were metabolized to Metabolite X and GS-8373. GS-17394
metabolized to the Metabolite LX. Apparent intracellular half-lives were similar for all
metabolites in all cell types (7-12 hr). A persistence of Total Acid Metabolites of Protease

10   Inhibitor Prodrugs in Stimulated (A), Quiescent PBMC (B) and MT-2 Cells (C) (1 hr, 10 uM
Pulse, 24 hr Chase) was observed.

2. Uptake and Persistence in Stimulated and Quiescent T-cells

Since HIV mainly targets T-lymphocytes, it is important to establish the uptake, metabolism

15   and persistence of the metabolites in the human T-cells. In order to estimate the relative
intracellular levels of the different PI prodrugs, GS-16503, 16571 and 17394 were incubated
at 10 µM for 1 hr with quiescent and stimulated T-cells (pulse phase). The prodrugs were
compared with a non-prodrug PI, nelfinavir. After incubation, the cells were washed,
resuspended in the cell culture media and incubated for 4 hr (chase phase). At specific time

points, the cells were washed, lysed and the lysates were analyzed by HPLC with UV detection. The sample preparation and analysis were similar to the ones described for MT-2 cells, quiescent and stimulated PBMC.

5   Table 5 demonstrate the levels of total acid metabolites and corresponding prodrugs in T-cells following pulse/chase and continuous incubation. There was significant cell uptake/metabolism in T-lymphocytes. There was no apparent difference in uptake between stimulated and quiescent T-lymphocytes. There was significantly higher uptake of phosphonate PI's than nelfinavir. GS17394 demonstrates higher intracellular levels than
10   GS16571 and GS16503. The degree of conversion to acid metabolites varied between different prodrugs. GS-17394 demonstrated the highest degree of conversion, followed by GS-16503 and GS-16571. The metabolites, generally, were an equal mixture of the mono-phosphonic acid metabolite and GS-8373 except for GS-17394, where Metabolite LX was stable, with no GS-8373 formed.

15

Table 5. Intracellular Levels of Metabolites and Intact Prodrug Following Continuous and 1 hr Pulse/4 hr Chase Incubation (10 μM/0.7 mLn cells/1 mL) of 10 μM PI Prodrugs and Nelfinavir with Quiescent and Stimulated T-cell

| | | Continuous Incubation | | | | 1 hr Pulse /4 hr Chase | | | |
| | | Quiescent T-cells | | Stimulated T-cells | | Quiescent T-cells | | Stimulated T-cells | |
Compound	Time (h)	Acid Met (μM)	Prodrug (μM)	Acid Met (μM)	Prodrug (μM)	Acid Met (μM)	Prodrug (μM)	Acid Met (μM)	Prodrug (μM)
	0	1180	42	2278	0	2989	40	1323	139
16503	2	3170	88	1083	116	1867	4	1137	31
	4	5262	0	3198	31	1054	119	1008	0
	0	388	1392	187	1417	1042	181	858	218
16571	2	947	841	1895	807	1170	82	1006	35
	4	3518	464	6147	474	1176	37	616	25
	0	948	1155	186	1194	4480	14	2818	10
17394	2	7231	413	3748	471	2898	33	1083	51
	4	10153	167	3867	228	1548	39	943	104
	0		101		86		886		1239
Nelfinavir	2		856		846		725		770
	4		992		1526		171		544

20

3. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in MT-2 Cells at 10, 5 and 1 μM.

To were similar to the determine if the cell uptake/metabolism is concentration dependent, selected PI's were incubated with the 1 mL of MT-2 cell suspension (2.74 mLn cells/mL) for 1 hr at 37°C at 3 different concentrations: 10, 5 and 1 μM. Following incubation, cells were washed twice with the cell culture medium, lysed and assayed using HPLC with UV detection. The sample preparation and analysis ones described for MT-2 cells, quiescent and stimulated PBMC. Intracellular concentrations were calculated based on cell count, a published single cell volume of 0.338 pl for MT-2 cells, and concentrations of analytes in cell lysates. Data are shown in Table 6.

Uptake of all three selected PI's in MT-2 cells appears to be concentration-independent in the 1-10 μM range. Metabolism (conversion to acid metabolites) appeared to be concentration-dependent for GS-16503 and GS-16577 (3-fold increase at 1 μM vs. 10 μM) but independent for GS-17394 (monolactate). Conversion from a respective metabolite X to GS-8373 was concentration-independent for both GS-16503 and GS-16577 (no conversion was observed for metabolite LX of GS-17394).

Table 6. Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in MT-2 Cells at 10, 5 and 1 μM.

Compound	Extracellular Concentration, μM	Cell-Assosiated Prodrug and Metabolites Concentration, μM				% Conversion to acid metabolites
		Metabolite X	GS8373	Prodrug	Total	
GS-17394	10	1358	0	635	1993	68
	5	916	0	449	1365	67
	1	196	0	63	260	76
GS-16576	10	478	238	2519	3235	22
	5	250	148	621	1043	40
	1	65	36	61	168	64
GS-16503	10	120	86	1506	1712	12
	5	58	60	579	697	17
	1	12	18	74	104	29

* For GS16576, Metabolite X is mono-aminobutyric acid

4. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in Human Whole Blood at 10 µM.

In order to estimate the relative intracellular levels of the different PI prodrugs under conditions simulating the in vivo environment, compounds representative of three classes of phosphonate PI prodrugs – bisamidate phosphonate (GS-16503), monoamidate phenoxy phosphonate (GS-16571) and monolactate phenoxy phosphonate(GS-17394) were incubated at 10 µM for 1 hr with intact human whole blood at 37°C. After incubation, PBMC were isolated, then lysed and the lysates were analyzed by HPLC with UV detection. The results of analysis are shown in Table 7. There was significant cell uptake/metabolism following incubation in whole blood. There was no apparent difference in uptake between GS-16503 and GS-16571. GS-17394 demonstrated significantly higher intracellular levels than GS-16571 and GS-16503.

The degree of conversion to acid metabolites varies between different prodrugs after 1 hr incubation. GS-17394 demonstrated the highest degree of conversion, followed by GS-16503 and GS-16571 (Table 7). The metabolites, generally, were an equimolar mixture of the mono-phosphonic acid metabolite and GS-8373 (parent acid) except for GS-17394, where Metabolite LX was stable with no GS-8373 formed.

Table 7. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in Human Whole Blood at 10 µM (Mean ± SD, N=3).

GS#	Intracellular Prodrug and Metabolites Concentration, µM			Major Intracellular Metabolites
	Acid Metabolite	Prodrug, µM	Total, µM	
16503	279 ± 47	61 ± 40	340 ± 35	X , GS-8373
16571	319 ± 112	137 ± 62	432 ± 208	X, GS-8373
17394	629 ± 303	69 ± 85	698 ± 301	LX

*   PBMC Intracellular Volume = 0.2 µL/mln

5. Distribution of PI Prodrugs in PBMC

5   In order to compare distribution and persistence of PI phosphonate prodrugs with those of
non-prodrug PI's, GS-16503, GS-17394 and nelfinavir, were incubated at 10 µM for 1 hr with
PBMC (pulse phase). After incubation, the cells were washed, resuspended in the cell culture
media and incubated for 20 more hr (chase phase). At specific time points, the cells were
washed and lysed. The cell cytosol was separated from membranes by centrifugation at 9000
10 xg. Both cytosol and membranes were extracted with acetonitrile and analyzed by HPLC
with UV detection.

Table 8 shows the levels of total acid metabolites and corresponding prodrugs in the cytosol
and membranes before and after the 22 hr chase. Both prodrugs exhibited complete
15 conversion to the acid metabolites (GS-8373 and X for GS-16503 and LX for GS-17394,
respectively). The levels of the acid metabolites of the PI phosphonate prodrugs in the
cytosol fraction were 2-3-fold greater than those in the membrane fraction after the 1 hr pulse
and 10-fold greater after the 22 hr chase. Nelfinavir was present only in the membrane
fractions. The uptake of GS-17394 was about 3-fold greater than that of GS-16503 and 30-
20 fold greater than nelfinavir. The metabolites were an equimolar mixture of metabolite X and
GS-8373 (parent acid) for GS-16503 and only metabolite LX for GS-17394.

Table 8. Uptake and Cell Distribution of Metabolites and Intact Prodrugs Following Continuous and 1 hr Pulse/22 hr Chase Incubation of 10 μM PI Prodrugs and Nelfinavir with Quiescent PBMC.

GS#	Cell Type	Fraction	Cell-Associated PI, pmol/mln cells			
			1 hr Pulse/ 0 hr Chase		1 hr Pulse/ 22 hr Chase	
			Acid Metabolites	Prodrug	Acid Metabolites	Prodrug
GS-16503	PBMC	Membrane	228	0	9	0
GS-16503	PBMC	Cytosol	390	0	130	0
GS-17394	PBMC	Membrane	335	0	26	0
GS-17394	PBMC	Cytosol	894	0	249	0
Nelfinavir	PBMC	Membrane		42		25
Nelfinavir	PBMC	Cytosol		0		0

Uptake and cell distribution of metabolites and intact prodrugs following 1 hr pulse/22 hr chase incubation of 10 μM PI prodrugs and Nelfinavir with quiescent PBMC were measured.

6. PBMC Extract/Dog Plasma/Human Serum Stability of Selected PI Prodrugs

The *in vitro* metabolism and stability of the PI phosphonate prodrugs were determined in PBMC extract, dog plasma and human serum (Table 9). Biological samples listed below (120 μL) were transferred into an 8-tube strip placed in the aluminum 37°C heating block/holder and incubated at 37°C for 5 min. Aliquots (2.5 μL) of solution containing 1 mM of test compounds in DMSO, were transferred to a clean 8-tube strip, placed in the aluminum 37°C heating block/holder. 60 μL aliquots of 80% acetonitrile/20% water containing 7.5 μM of amprenavir as an internal standard for HPLC analysis were placed into five 8-tube strips and kept on ice/refrigerated prior to use. An enzymatic reaction was started by adding 120 μL aliquots of a biological sample to the strip with the test compounds using a multichannel pipet. The strip was immediately vortex-mixed and the reaction mixture (20 μL) was sampled and transferred to the Internal Standard/ACN strip. The sample was considered the time-zero sample (actual time was 1-2 min). Then, at specific time points, the

reaction mixture (20 μL) was sampled and transferred to the corresponding IS/ACN strip. Typical sampling times were 6, 20, 60 and 120 min. When all time points were sampled, an 80 μL aliquot of water was added to each tube and strips were centrifuged for 30 min at 3000xG. The supernatants were analyzed with HPLC under the following conditions:

5

Column: Inertsil ODS-3, 75 x 4.6 mm, 3 μm at 40°C.

Mobile Phase A: 20 mM ammonium acetate in 10%ACN/90%water

Mobile Phase B 20 mM ammonium acetate in 70%ACN/30%water

Gradient: 20% B to 100% B in 4 min, 2 min 100% B, 2 min 20% B

10   Flow Rate: 2 mL/min

Detection: UV at 243 nm

Run Time: 8 min

The biological samples evaluated were as follows:

15   PBMC cell extract was prepared from fresh cells using a modified published procedure (A. Pompon, I. Lefebvre, J-L. Imbach, S. Kahn, and D. Farquhar, Antiviral Chemistry & Chemotherapy, 5, 91 - 98 (1994)). Briefly, the extract was prepared as following: The cells were separated from their culture medium by centrifugation (1000 g, 15 min, ambient temperature). The residue (about 100 μL, 3.5 x 10^8 cells) was resuspended in 4 mL of a

20   buffer (0.010 M HEPES, pH 7.4, 50 mM potassium chloride, 5 mM magnesium chloride and 5 mM dl-dithiothreitol) and sonicated. The lysate was centrifuged (9000 g, 10 min, 4°C) to remove membranes. The upper layer (0.5 mg protein/mL) was stored at –70°C. The reaction mixture contained the cell extract at about 0.5 mg protein/mL.

Human serum (pooled normal human serum from George King Biomedical Systems, Inc.).
25   Protein concentration in the reaction mixture was about 60 mg protein/mL.

Dog Plasma (pooled normal dog plasma (EDTA) from Pel Freez, Inc.). Protein concentration in the reaction mixture was about 60 mg protein/mL.

Table 9:   **PBMC Extract/Dog Plasma/Human Serum Stability of Selected PI Prodrugs**

GS#	PBMC Extract[1] $T_{1/2}$, min	Dog Plasma $T_{1/2}$, min	Human Serum $T_{1/2}$, min	HIV EC_{50} (nM)
16503	2	368	>>400	6.0 ± 1.4
16571	49	126	110	15 ± 5
17394	15	144	49	20 ± 7

5

Example Section P

Table 10:   Enzymatic and Cellular data

Formula II ALPPI activity

Amprenavir

94-003
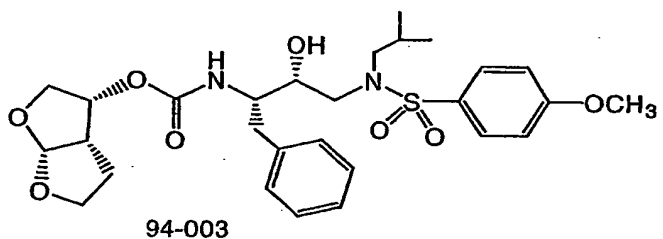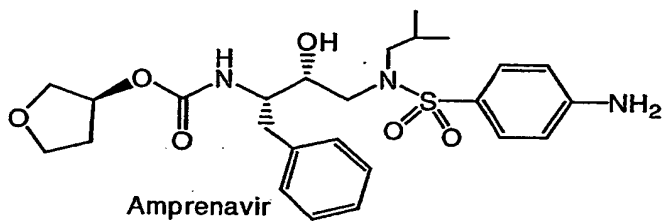
Ki [pM]
≤ 10   +++
> 10 to ≤ 100   ++
> 100 to ≤ 1,000   +
> 1,000   -

EC$_{50}$ [nM]
≤ 50   +++
> 50 to ≤ 500   ++
> 500 to ≤ 5,000   +
> 5,000   -

I50V and I84V/L90M fold change
> 30   +++
> 10 to ≤ 30   ++
> 3 to ≤ 10   +
≤ 3   -

CC$_{50}$ [µM]
≤ 5   ++
> 5 to ≤ 50   +
> 50   -

Compound	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L90M fold change	CC$_{50}$ (μM)
Saquinavir	++	+++	–	–	+++	
Nelfinavir	+	+++	–	+	+++	
Indinavir	+	+++	–	+	+++	
Ritonavir	++	+++	++	++	+++	
Lopinavir	++	+++	++	+++	++	
Amprenavir	+	+++	+++	+++	++	–
Atazanavir	++	+++	–	–	+++	
Tipranavir	++	++	–	–	+	
94-003	+++	+++	+++	+++	++	+
TMC114	+++	+++	++	++	–	

P1-Phosphonic acid and esters

R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ (µM)
OH	OH	+++	+	–	–	–
OMe	OMe	++	+++			
OEt	OEt	+++	+++	–	–	+
OCH$_2$CF$_3$	OCH$_2$CF$_3$	++	–			
OiPr	OiPr	++	+++	–	–	
OPh	OPh		+++			
OMe	OPh	++	+++			
OEt	OPh	+++	+++			
OBn	OBn	++	+++	–	–	+
OEt	OBn	++	+++			++
OPoc	OPoc		+			
OH	OEt		++			
OH	OPh	+++	–			
OH	OBn		+	–	–	

5

P1-Phosphonic acid and esters

5

R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ (μM)
OH	OH	+++	+			
Et	Et	+++	+++			

P1-Direct phosphonic acid and esters

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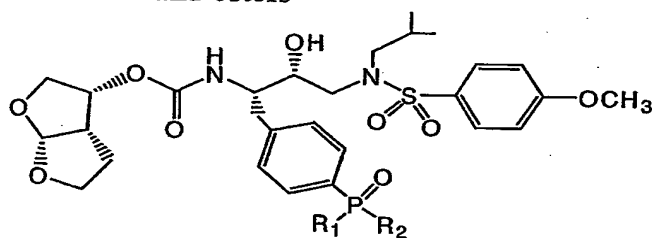
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
OH	OH	++	−			
OEt	OEt	+++	+++	+	−	

-1608-

P1-CH₂-phosphonic acid and esters

5
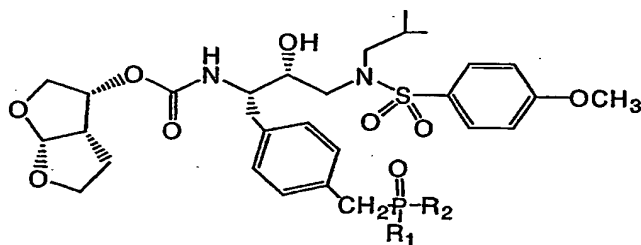
R1	R2	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC₅₀ μM
OE	OE	+++	+++	+	+	

P1-P-Bisamidates
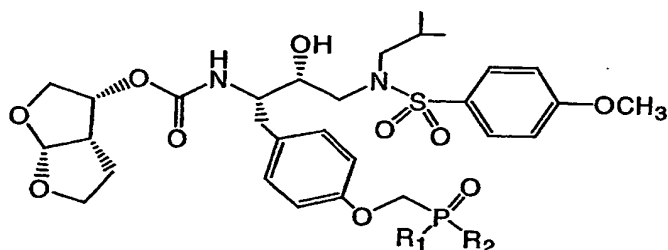
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
NHEt	NHEt	+++	++	−	−	
Gly-Et	Gly-Et	++	++			
Gly-Bu	Gly-Bu	+++	+++			
Ala-Et	Ala-Et	++	++		−	−
Ala-Bu	Ala-Bu	++	+++	+	−	
Aba-Et	Aba-Et	+++	+++			
Aba-Bu	Aba-Bu	+++	+++	++	+	
Val-Et	Val-Et	+	+++	−	−	
Leu-Et	Leu-Et	++	+++			
Leu-Bu	Leu-Bu	++	++	+	+	
Phe-Et	Phe-Et		+++			
Phe-Bu	Phe-Bu		+++			

5

P1-P-Bislactates
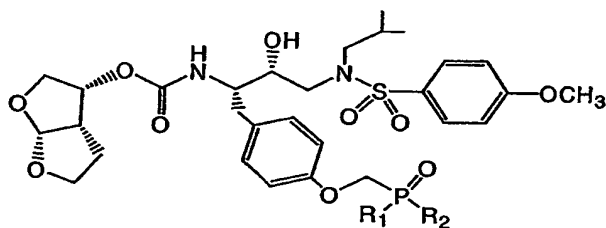
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
Glc-Et	Glc-Et	+++	+	−	−	
Lac-Et	Lac-Et	++	++	−	−	
Lac-iPr	Lac-iPr	++	+++		−	

P1-P-Monoamidates
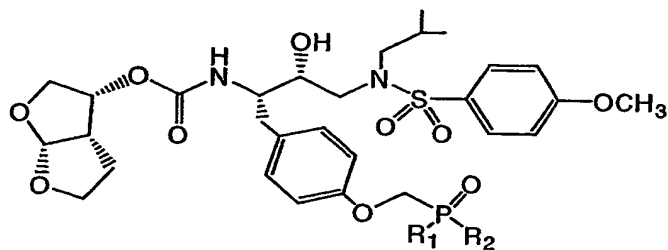
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
OPh	Gly-Bu	++	++	−	−	
OPh	Ala-Me	++	+++		−	
OPh	Ala-Et	+++	+++	−	−	
OPh	Ala-iPr	++	+++	−	−	
OPh	Ala-iPr	+++	+++			
OPh	Ala-iPr	++	+++			
OPh	(D)Ala-iPr	++	+++		−	
OPh	(D)Ala-iPr	+++	+++			
OPh	(D)Ala-iPr	+++	+++			
OPh	Ala-Bu	++	+++	−	−	
OPh	Ala-Bu	++	+++	−		
OPh	Ala-Bu	++	+++	−		
OPh	Aba-Et		+++			
OPh	Aba-Et		+++	−	−	
OPh	Aba-Et		++			
OPh	Aba-Bu		+++	+	−	
OPh	Aba-Bu		++ .	−	−	
OBn	Ala-Et	+++	+++	−	−	
OH	Ala-OH	+++	−			
OH	Ala-Bu		−			

P1-P-Monolactates (1)
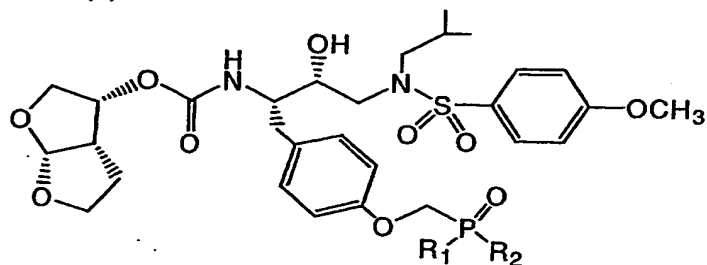
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L90M fold change	CC$_{50}$ μM
OPh	Glc-Et	+++	+++	−		−	
OPh	Lac-Me		++	−			
OPh	Lac-Et		+++	−	+	−	+
OPh	Lac-Et	+++	+++	−		−	
OPh	Lac-Et	++	+++	−		−	
OPh	Lac-iPr	++	+++	−		−	
OPh	Lac-iPr	+++	+++				
OPh	Lac-iPr	++	+++				
OPh	Lac-Bu	++	++				
OPh	Lac-Bu	++	++			−	
OPh	Lac-Bu	++	++				
OPh	Lac-EtMor		−				
OPh	Lac-PrMor		−				
OPh	(R)Lac-Me	+++	+++				
OPh	(R)Lac-Et	+++	+++	−		−	
OEt	Lac-Et		++				
OCH$_2$CF$_3$	Lac-Et		++				
OBn	Lac-Bn	++	++				
OBn	(R)Lac-Bn						
OH	Lac-OH	+++	+			−	
OH	(R)Lac-OH	++	+			−	

P1-P-Monolactates (2)

5
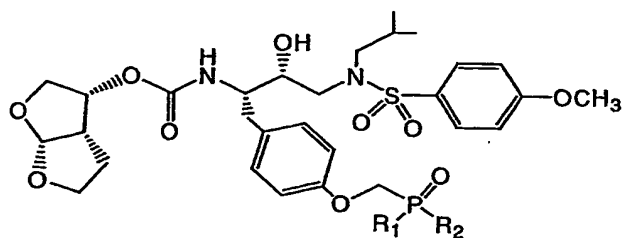
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
OPh	mix-Hba-Et	++	+++	+	−	
OPh	(S)Hba-Et	+	+++			
OPh	(S)Hba-tBu		+++			
OH	(S)Hba-OH	++				
OPh	(R)Hba-Et		+++			
OPh	(S)MeBut-Et		+++			
OPh	(R)MeBut-Et		+++			
OPh	DiMePro-Me	++				
OPh	(S)Lac-EtMor		−			
OPh	(S)Lac-PrMor		−			
OPh	(S)Lac-EtPip		++	−	−	

P1-P-Monolactates (3)
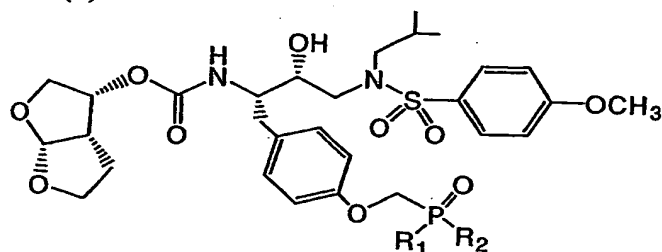
R1	R2	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 μM
OPh—o-i-But	(S)Lac-Et		+++			
OPh—p-n-Oct	(S)Lac-Et		++			
OPh—p-n-But	(S)Lac-Et		+++			
OPh-m-COOBn	(S)Lac-Et		++			
OPh-m-COOH	(S)Lac-Et		++			
OPh-m-CH2OH	(S)Lac-Et		++	−	−	
OPh-m-CH2NH2	(S)Lac-Et	++	++			
OPh-m-CH2NMe2	(S)Lac-Et		+			
OPh-m-CH2Mor	(S)Lac-Et		++	−	−	
OPh-m-CH2Pip	(S)Lac-Et		++			
OPh-m-CH2NMeC2OM	(S)Lac-Et		++			
OPh-o-OEt	(S)Lac-Et		+++			
ONMe2	(S)Lac-Et		++			
OPip	(S)Lac-Et		+			
OMor	(S)Lac-Et		−			

5

P1-C$_2$H$_4$-P-Monolactates

5
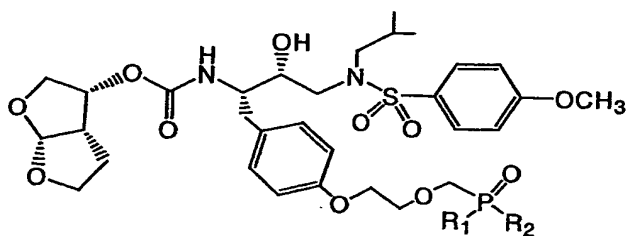
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
-OC$_2$H$_4$OBn			+++			
OEt	OEt		+++	–	–	
OPh	Lac-Et		++	–	–	
OH	OH	++				
OH	Lac	++				

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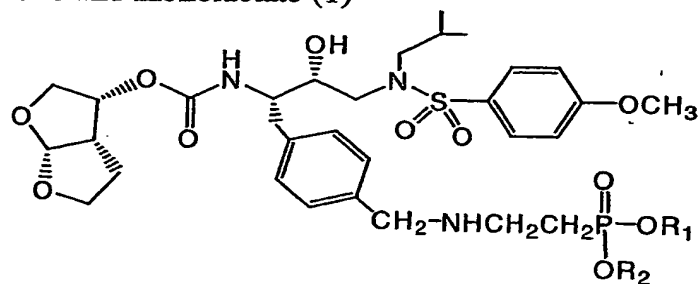
R₁	R₂	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L9M fold change	CC₅₀ μM
Et	Et	++	+++		−		
H	H	++	-		+		
Ph	Lac-Et		++	−	++	−	
Ph	Lac-Et		+		+	−	−
Ph	Lac-Et		+		++	−	
Ph	Aba-Et		+		+	−	
Ph-oEt	Lac-Et	++	++	−	++	−	
Ph-dM	Lac-Et		+++		+.	+	
Ph-dM	Lac-Pr		+++				
H	Lac	++					
Ph	Hba-Et		++		++	−	
Ph	Hba-Et		++		++	−	+
Ph	Hba-Et		++		++	−	
H	Hba	+					

P1-CH$_2$N-P-diester and monolactate (2)

5
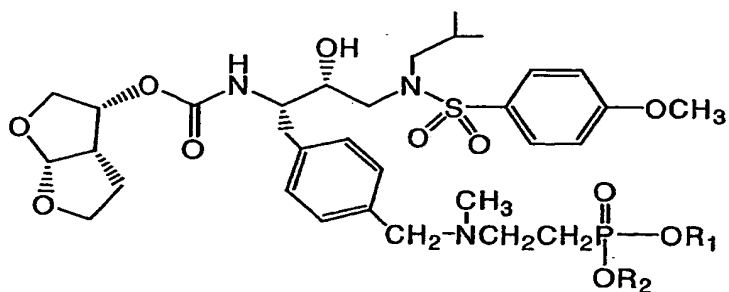
R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$μM
Ph	Lac-Et	+	++	+	+	
H	H	++				

P1-CH$_2$N-P-diester and monolactate (3)

10
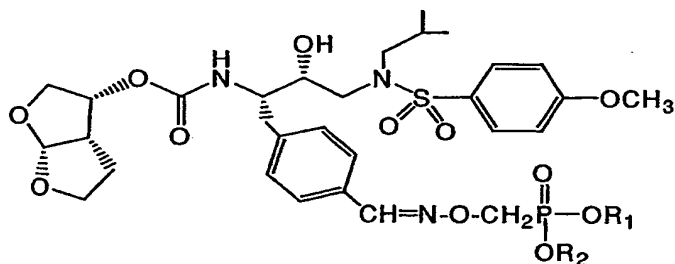
R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$μM
Et	Et	++	+++		−	

P1-N-P1-Phosphonic acid and esters (1)

R1	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ µM
piperazine–CH$_2$CH$_2$–P(=O)(OEt)(OEt)	−	++			
piperidine–O–CH$_2$–P(=O)(OEt)(OEt)	−	++			
tetrahydropyridine–N–CH$_2$–P(=O)(OH)(OH)	−				
tetrahydropyridine–N–CH$_2$–P(=O)(OEt)(OEt)	++	+++		+	
–N–CH$_2$–P(=O)(OPh)(Lac-Et)		−			
–N–CH$_2$–P(=O)(OH)(Lac)	−				
–N–C$_2$H$_4$–P(=O)(OMe)(OMe)	+	++			
–N–C$_2$H$_4$–P(=O)(OBn)(OBn)	++	+++		+	
–N–C$_2$H$_4$–P(=O)(OPh)(Lac-Et)		−			
–N–C$_2$H$_4$–P(=O)(OH)(Lac)		−			
–N–C$_2$H$_4$–P(=O)(OH)(OH)	−				
–N–C$_2$H$_4$–P(=O)(OEt)(OEt)	+	+++		+	

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P1-N-P1-Phosphonic acid and esters (2)

R1	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
HN—C$_6$H$_4$—P(=O)(OH)(OH)	+	+		+	
HN—C$_6$H$_4$—P(=O)(OEt)(OEt)	++	+++		+	
HN—C$_6$H$_4$—P(=O)(OBn)(OBn)	++	+++			
HN—C$_6$H$_4$—P(=O)(Ala-Et)(Ala-Et)	++	++		−	
HN—C$_6$H$_4$—P(=O)(OPh)(Lac-Et)		+++			
Me-N—C$_6$H$_4$—P(=O)(OEt)(OEt)	++	+++		+	
Me-N—C$_6$H$_4$—P(=O)(OPh)(Lac-Et)		+++		−	
HN—CH$_2$—C$_6$H$_4$—P(=O)(OEt)(OEt)	−	+++		++	
HN—CH$_2$—C$_6$H$_4$—P(=O)(OH)(OH)	−				
N—CH$_2$—C$_6$H$_4$—P(=O)(OEt)(OEt)	+	+++	+++	−	
N—CH$_2$—C$_6$H$_4$—P(=O)(OH)(OH)	−				
N—CH$_2$—C$_6$H$_4$—P(=O)(OPh)(Lac-Et)		+++	++	+	
N—CH$_2$—C$_6$H$_4$—P(=O)(OH)(Lac)	−				

P1-N-P1-Phosphonic acid and esters (3)

R1	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
	++	+++	+	+	
	+	++	+	+	
	+	++	+	+	
	+				
	−	−			

5

P1-N-P1-Phosphonic acid and esters (4)

R1	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
NHCH$_2$—P(=O)(OH)(OH)	+++				
NHCH$_2$—P(=O)(OEt)(OEt)	+++	+++	–	–	
NHCH$_2$—P(=O)(OBn)(OBn)	++	+++	+	–	
NHCH$_2$—P(=O)(OPh)(Ala-iPr)	++	+++			
NHCH$_2$—P(=O)(OPh)(Ala-iPr)	++	++			
NHCH$_2$—P(=O)(OPh)(Ala-iPr)	+++	+++			
NHC$_2$H$_4$—P(=O)(OPh)(Lac-Et)		+++	++	–	
NHC$_2$H$_4$—P(=O)(OPh)(Lac-Et)		+++	++	–	
NHC$_2$H$_4$—P(=O)(OH)(OH)	++				
NHC$_2$H$_4$—P(=O)(OH)(Lac)	++				

P1- P-cyclic monolactate

5
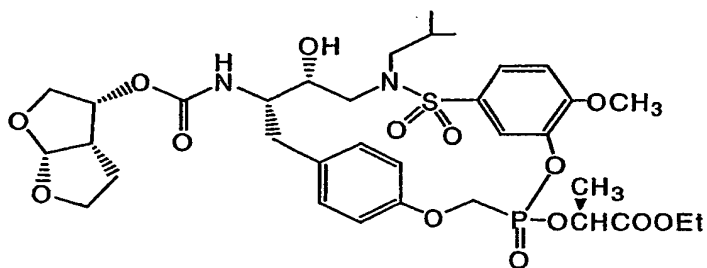
R₁	R₂	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC₅₀μM
		nd	nd			
		nd	nd			

10

P1'-N-P1-Phosphonic acid and esters

R1	R2	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 μM
CH₃	(structure)	++	+++	++	+	
OH	(structure)		+++	–	–	
CH₂OH	(structure)	+++	+++	–	–	
OBn	(structure)	+++	+++	–	–	
OH	(structure)	–	++	–	–	
OBn	(structure)	–	+++		–	
(phosphonic acid structure)	(morpholine)	–	–	+	+	
(phosphonic ester structure)	(morpholine)	+	++	+	+	
OH	(piperidine NH)	–	–			
(phosphonic structure)	(NCHO)	++	–			
(phosphonic structure)	(NCHO)	++	–			
(phosphonic structure)	(NCHO)	++	++			
(phosphonic structure)	(NCH₃)	+	–			i

5

P1'-Phosphonic acid and esters

R1	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 μM
(benzyl)	++	+++	+++	+++	
(C(CH3)2CH2OH)	+++	+++	+++	+++	
(O-CH2-P(=O)(OH)OH)	++	+		+++	
(O-CH2-P(=O)(OEt)OEt)	+++	+++		+++	
(O-CH2-P(=O)(OBn)OBn)	+++	+++		++	
(O-CH2CH2-P(=O)(OH)OH)	++	++	++	++	
(O-CH2CH2-P(=O)(OBn)OBn)	++	+++	+++	+++	

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P2-Monofuran-P1-phosphonic acid and esters
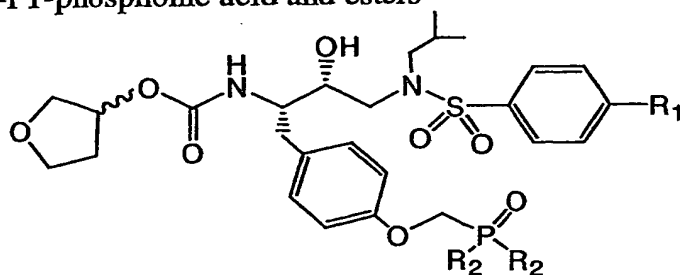
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ µM
OMe	OH		–	+++	+++	
OMe	OEt	+++	+++	+++	++	
OMe	OBn		+++	++	++	
OMe	phenol	+++	+++	+++	+	
OMe	OEt	++	+++	+++	++	
NH$_2$	phenol	+	++	+	–	
NH$_2$	OH		–		+	
NH$_2$	OBn	++	++		+	

5

P2-Monofuran-P1-P-monoamidates

R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ µM
OPh	Ala-iPr	++	++		+	
OPh	Ala-iPr	++	++			
OPh	Ala-iPr	+	++			

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P2-Other modifications-P1-phosphonic acid and esters
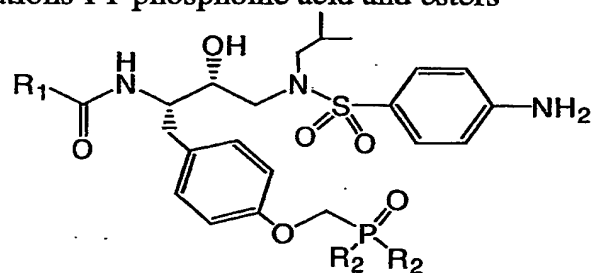
R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ µM
<image>	phenyl	+	+++	+++	++	
<image>	phenol	+	++	++	+	
<image>	OH	–	–	++	–	
<image>	OBn	+	++	+	–	
<image>	phenyl	+	++	+++	+	
<image>	OH	+	–	++	+	
<image>	OBn	+	++	+++	+	
<image>	phenyl	–	++		++	
<image>	phenol	+	+		–	
<image>	OH	+	–	–	–	
<image>	OBn	++	++	+	–	

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P2'-Amino-P1-phosphonic acid and esters
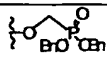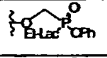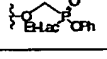
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R1	R2	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
OH	p-NH$_2$	++	++	–	–	
(phosphonic, HO OH)	p-NH$_2$	++	–	+	–	
(phosphonic, EtO OEt)	p-NH$_2$	++	+++	.	–	
(phosphonic, EtO OEt)	p-NO$_2$	++	+++		–	
(phosphonic, EtO OEt)	p-NHEt	++	+++		–	
(phosphonic, BnO OBn)	p-NH$_2$	++	+++	–	–	
OH	m-NH$_2$	++	++		–	
(phosphonic, HO OH)	m-NH$_2$	++	+		–	
(phosphonic, EtO OEt)	m-NH$_2$	++	++		–	
(phosphonic, BnO OBn)	m-NH$_2$	++	+++	–	–	
(phosphonic, BuH$_2$ OPh)	m-NH$_2$	+	++	–	–	.
(phosphonic, BuH$_2$ OPh)	m-NH$_2$	++	++			
(phosphonic, BuH$_2$ OPh)	m-NH$_2$	+	++			

P2'-Substituted-P1-phosphonic acid and esters (1)

R1	X	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 μM
(structure: HO OH)	p-OH	+++	+			
(structure: EtO OEt)	p-OH	+++	+++			
(structure: LacO OH)	p-OH	++				
(structure: Et-Lac OPh)	p-OH		+++		–	
(structure: Et-Lac OPh)	p-OBn		++			
(structure: Bn-Lac OBn)	p-OBn		–			
(structure: HO OH)	p-H	++	–			
(structure: BnO OBn)	p-H	++	+++		+	
(structure: Et-Lac OPh)	p-H		+++	+	+	
(structure: Bn-Lac OBn)	p-H		++			
(structure: Lac OH)	p-H	++				
(structure: HO OH)	p-F	++	+			
(structure: BnO OBn)	p-F	++	+++		+	
(structure: Et-Lac OPh)	p-F		+++	+	+	
(structure: Bn-Lac OBn)	p-F		++	+	+	
(structure: Lac OH)	p-F	++				
(structure: HO OH)	p-CF3	+++	+			
(structure: BrO OBn)	p-CF3	++	+++		–	
(structure: HO OH)	p-OCF3	++	+			
(structure: BrO OBn)	p-OCF3	++	+++		+	

	p-CN	++	+++		–	
	p-Pip	–	–			
	p-Pip-Me	–	–			

P2'-Substituted-P1-phosphonic acid and esters (2)

R1	X	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 μM
[structure: BnO, OBn]	m-Py	++	+++			
[structure: HO, OH]	m-Py	++				
[structure: BnLac, OPh]	m-Py	++	++	+	−	
[structure: BnLac, OBn]	m-Py	++	++			
[structure: Lac, OH]	m-Py	++				
[structure: BnO, OBn]	m-Py-Me⁺		+			
[structure: BnLac, OPh]	m-Py-Me⁺		++			
[structure: BnO, OBn]	m-Py-oxide		++			
[structure: HO, OH]	m-Py-oxide	++				
[structure: BnLac, OPh]	m-Py-oxide	++	++		−	
[structure: Lac, OH]	m-Py-oxide	+				
[structure: BnLac, OBn]	m-Py-oxide		−			
p-Py-oxide	p-OMe	++	−			
[structure: BnLac, OPh]	p-CHO		+++			
[structure: BnO, OBn]	p-CHO		+++			
[structure: BnLac, OPh]	p-CH2 OH		+++	−	−	
[structure: Lac, OH]	p-CH2 OH	++				
[structure: HO, OH]	p-CH2 OH	++				
[structure: BnLac, OPh]	p-CH2 Mor		++	−	−	
[structure: Lac, OH]	p-CH2 Mor	−				
[structure: HO, OH]	p-CH2 Mor	−				

P2'-Alkylsulfonyl-P1-phosphonic acid and esters

R1	X	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 µM
(structure)	(structure)	–	–			
(structure)	(structure)	+	++			
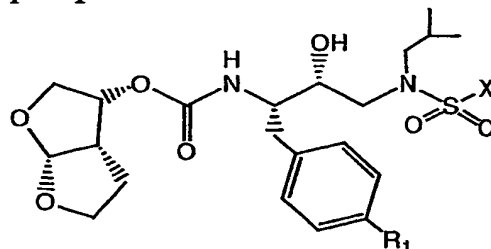
P2'-Carbonyl-substituted-P1-phosphonic acid and esters

R1	X	Ki (pM)	EC50 (nM)	I50V (#1) fold change	I84V/L90M fold change	CC50 µM
(structure)	(structure)	–				
(structure)	(structure)	–	++			
(structure)	(structure)		+			

P2'-Phosphonic acid and esters

R	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
phenyl–OH	+++	+++	–	–	
phenyl–O–CH$_2$–P(=O)(OH)(OH)	+++	+	–	–	
phenyl–O–CH$_2$–P(=O)(OH)(OPh)	++	–			
phenyl–O–CH$_2$–P(=O)(OEt)(OEt)	++	+++	++	++	
phenyl–O–CH$_2$–P(=O)(OBn)(OBn)	+	++	+++	+++	
phenyl–OH	+++	+++	+	+	
phenyl–OMe	+++	+++	+++	++	
phenyl–O–CH$_2$–P(=O)(OH)(OH)	++	++	++	+	
phenyl–O–CH$_2$–P(=O)(OEt)(OEt)	+++	+++	+++	++	
phenyl–O–CH$_2$–P(=O)(OBn)(OBn)	++	+++	++	++	
phenyl–OMe, OH	+++	+++	–	–	
phenyl–OMe, O–CH$_2$–P(=O)(OH)(OH)	+++	++	+	–	
phenyl–OMe, O–CH$_2$–P(=O)(OEt)(OEt)	+	++	+	+	
phenyl–OMe, O–CH$_2$–P(=O)(OBn)(OBn)	–	+	+++	++	
phenyl–OH, O–CH$_2$–P(=O)(OEt)(OEt)	+	++	+	–	

P2'-P-Bisamidate, monoamidate, and monolactate
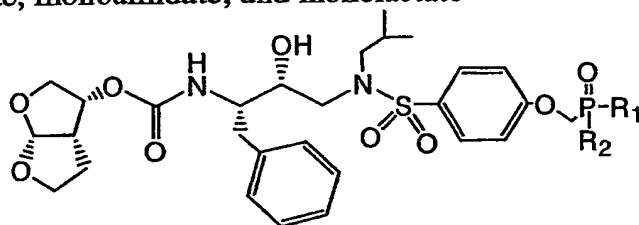
R₁	R₂	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC₅₀ µM
Ala-Bu	Ala-Bu	+	++	+	+	
OPh	Ala-iPr	++	++			
OPh	Lac-iPr	+	+			
OH	Ala-OH	++				

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P1-N-P2'-Phosphonic acid and esters
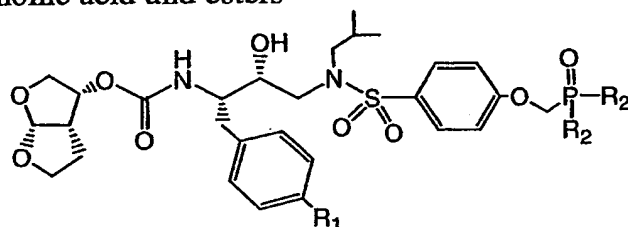
R₁	R₂	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC₅₀ µM
NO₂	phenol		+++	−		
NH₂	OH	++	-			
NH₂	OEt	+	++	...	++	
NH₂	OBn	+	+		+	
NMe₂	OEt	++	+++		++	
OH	OH	++	-			
OH	OBn	++	++			
OC₂H₄NMe₂	OH	+++	+			
OC₂H₄-NMe₂	OBn	++	++			

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P1-N-P2'-P-Bisamidate and monoamidate

R₁	R₂	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC₅₀ μM
Ala-Bu	Ala-Bu	+	+			
OPh	Ala-iPr	+	−			
OPh	Ala-iPr	++	−			

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P1-NEt-P2'-P-Bisamidate and monoamidate
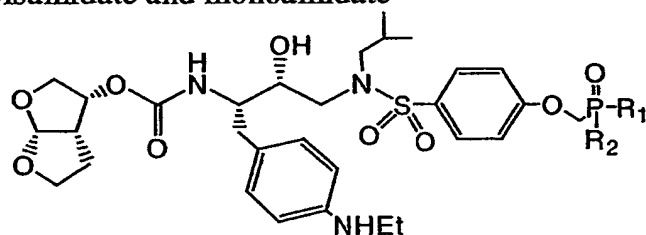
R₁	R₂	Ki (pM)	EC₅₀ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC₅₀ μM
OPh	Ala-iPr	+	+			
OPh	Ala-iPr	+	+	−	−	

10

Phosphate prodrug of ampenavir
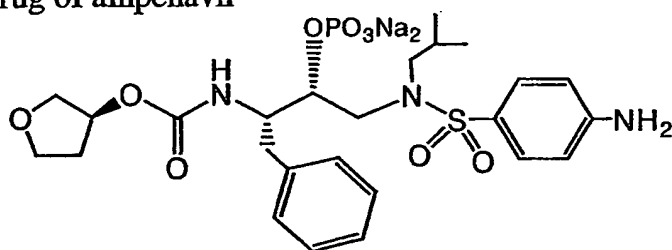
R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
			++			

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Phosphate prodrug of 94-003
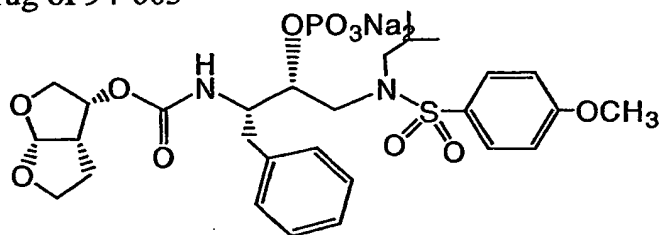
R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
			+++			

10   Phosphate prodrug of GS77366 (P1-mono(S)Lac-iPr)

R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
			+++			

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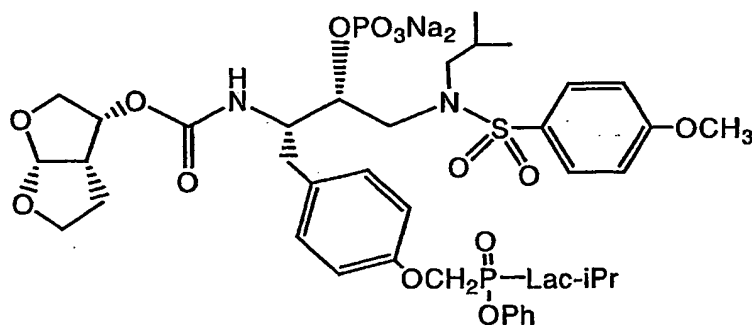
Valine prodrug of (P1-mono(S)Lac-Et)
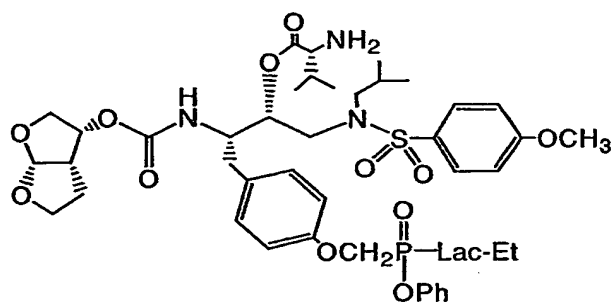
R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
			++			

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Valine prodrug of GS278053 (P1-mono(S)Lac-Et,P2'-CH$_2$OH)

10
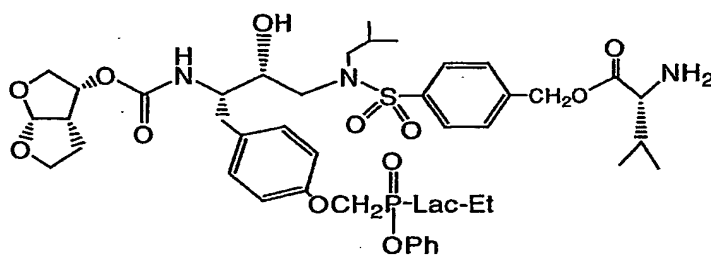
R$_1$	R$_2$	Ki (pM)	EC$_{50}$ (nM)	I50V (#1) fold change	I84V/L90M fold change	CC$_{50}$ μM
			++			

Table 11:   Enzymatic and Cellular Activity Data

Formula VIIIa CCLPPI activity
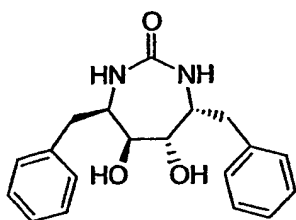
DMP-850

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Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC$_{50}$/ nM						
	K_i (nM)	WT IC$_{50}$/ nM	84V90M IC$_{50}$/ nM	WT	84V90M	30N 82I88D	48V54 V82A	48V54 V82S	48V82 A90M	46I50V
H (DMP-850)	0.033	3.0	9.1	165	819	82	82	73	45	88
p-OH	0.029	3.0	12	149	143	79	32	39	19	55
p-OBn	>5	353	781	2123	5312	1548	ND	ND	ND	ND
p-OCH$_2$PO$_3$Bn$_2$	>5	276	2042	2697	4963	2119	ND	ND	ND	ND
p-OCH$_2$PO$_3$Et$_2$	>5	627	1474	2480	>6000	1340	ND	ND	ND	ND
p-OCH$_2$PO$_3$H$_2$	>5	551	1657	>12000	ND	ND	ND	ND	ND	ND
m-OH	0.128	1.6	12	151	475	249	84			104
m-OBn	0.253	6.9	27	218	2422	82	709	ND	ND	601
m-OCH$_2$PO$_3$Bn$_2$ (N-iPr indazole)	1.54[a]	31	72	489	514	237	159	171	168	708
m-OCH$_2$PO$_3$Bn$_2$	0.177	18	43	898	>6000	705	2597	ND	ND	3121
m-OCH$_2$PO$_3$Et$_2$	1.93[a]	70	169	665	3005	93	513	ND	ND	857
m-OCH$_2$PO$_3$H$_2$	0.254	8.3	33	>12000	ND	ND	ND	ND	ND	ND

m-OCH₂PO₃Ph₂	0.543ᵃ	10	42	1349	>6000	1541	2183	ND	ND	3380
m-OCH₂PO₃HPh	0.644	17	65	1745	>6000	ND	ND	ND	ND	ND
m-mono-Ala-Bu	0.858ᵃ	6.6	39	1042	>6000	425	790	ND	ND	797
m-mono-Ala-Et¶		35	68	1436	>6000	219	734	ND	ND	1350
m-mono-Lac-Bu		15	34	2663	>6000	1089	ND	ND	ND	ND
m-mono-Lac-Et		23	80	2609	>6000	516	5923	ND	ND	>6000
m-bis-Ala-Bu	1.279ᵃ	18	103	1079	>6000	2362	1854	ND	ND	1536
m-bis-Ala-Et	1.987ᵃ	31	202	5620	>6000	1852	ND	ND	ND	ND

Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC$_{50}$/ nM						
	K_i (nM)	WT IC$_{50}$/ nM	84V90M IC$_{50}$/ nM	WT	84V90M	30N 82I88 D	48V5 4V82 A	48V54 V82S	48V82A 90M	46I50 V
H (DMP-850)	0.033	3.0	9.1	165	819	82	82	73	45	88
benzoic acid (CO-OH)	0.091	3.4	27	1548	>6000	>6000	ND	ND	ND	ND
benzamide-CH$_2$CH$_2$-PO$_3$Et$_2$	0.354	3.3	25	168	909	750	277			489
benzamide-CH$_2$CH$_2$CH$_2$-PO$_3$Et$_2$	0.157	1.6	10	188	476	666	240			319
benzamide-CH$_2$CH$_2$CH$_2$-PO$_3$Bn$_2$	0.044	5.0	27	491	387	234	238			192
benzamide-CH$_2$CH$_2$CH$_2$-PO$_3$H$_2$	0.362	7.3	70	5141	>6000	4480	ND	ND	ND	ND
benzamide-CH$_2$CH$_2$CH$_2$-P(OPh)(O-Lac-Et)=O	0.112	1.4	6.4	603	1276	678	208			209
benzamide-CH$_2$CH$_2$CH$_2$-P(OPh)(NH-Ala-Et)=O	<0.03	1.3	7.5	625	708	899	301			398
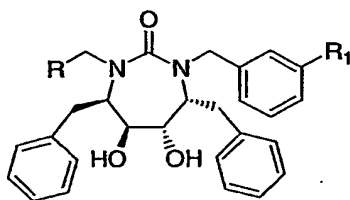
| Structure, R1 | Structure, R | Enzymatic assay | | | Cell-based assay (MT-4) EC$_{50}$/ nM | | | | | | |
		K_i (nM)	WT IC$_{50}$/ nM	84V90M IC$_{50}$/ nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82AS	48V82A90M	46I50V
CO$_2$H	[4-HO-phenyl]		15	174	3055	>6000	887	ND	ND	ND	ND
CONH(CH$_2$)$_3$PO$_3$Et$_2$	[4-HO-phenyl]	0.009	1.1	12	65	311	74	80	75	74	85
CO$_2$H	[3-H$_2$N-phenyl]		18	299	2344	>6000	3360	ND	ND	ND	ND
CONH(CH$_2$)$_3$PO$_3$Et$_2$	[3-H$_2$N-phenyl]	<0.004	2.3	29	176	824	171	233	ND	ND	195
CO$_2$H	[indazole]	0.091	3.4	27	1548	>6000	>6000	ND	ND	ND	ND
CONH(CH$_2$)$_3$PO$_3$Et$_2$	[indazole]	0.157	1.6	10	188	476	666	240			319

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	Enzymatic assay			Cell-based assay (MT-4) EC$_{50}$/ nM						
Structure, R	K_i (nM)	WT IC$_{50}$/ nM	84V90 M IC$_{50}$/ nM	WT	84V90 M	30N 82I88D	48V5 4V82 A	48V5 4V82 S	48V82 A90M	46I50 V
CH$_3$ (DMP-851)	0.033	3.8	9.4	54	918	69	33	30	22	17
OH	0.65[a]	6.1	77	356	2791	669	294	ND	ND	683
OCH$_2$PO$_3$Et$_2$	1.230[a]	23	157	356	>6000	145	175	ND	ND	138
OCH$_2$PO$_3$H$_2$	0.809	59	137	1074	>6000	ND	ND	ND	ND	ND
O-mono-Lac-Et	>2.0	93	553	>6000	>6000	ND	ND	ND	ND	ND
O-mono-Lac-Bu	>2.0	25	249	>6000	>6000	ND	ND	ND	ND	ND
CH$_2$OH	0.017	2.8	31	253	1106	486	413	ND	ND	524
CH$_2$OCH$_2$PO$_3$Et$_2$	2.8	13	123	119	3295	267	430	ND	ND	789
CH$_2$OCH$_2$PO$_3$H$_2$		42	205	1757	>4243	ND	ND	ND	ND	ND

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R	R1	R2	Enzymatic assay			Cell-based assay (MT-4) EC_{50}/ nM						
			K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50}/ nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
—	—	—	0.374	5.8	43.3	193	2312	281	705	ND	ND	772
H	Ph	H		34	631	2492	>600	3360	ND	ND	ND	ND
OH	Ph	OH		31	397	117	5609	756	2266	ND	ND	928
OH	Ph	OCH₂PO₃		9	40	33	791	92	807	1103	1429	53
H	Ph	OCH₂PO₃	0.656	3.9	48	107	2456	293	1438	1899	3292	589
H	Indazol	H	<0.01	2.5	13	11	22	<8	5.5	8	4	4.0
OH	Indazol	OH	0.012	0.6	3.5	>600	2728	7224	ND	ND	ND	ND
OH	Indazol	OCH₂PO₃	0.137	1.1	5.5	1698	1753	1998	ND	ND	ND	ND
H	Indazol	OCH₂PO₃	0.028	1.4	6.2	57	40	68	28	26	32	27

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R	R1	R2	Enzymatic assay			Cell-based assay (MT-4) EC$_{50}$/ nM						
			K_i (nM)	WT IC$_{50}$/ nM	84V90M IC$_{50}$/ nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
OH	Ph	OCH$_2$PO$_3$Et$_2$		9	40	33	791	92	807	1103	1429	53
H	Ph	OCH$_2$PO$_3$Et$_2$	0.656	3.9	48	107	2456	293	1438	1899	3292	589
OCH$_3$	Ph	OCH$_2$PO$_3$Et$_2$										
OH	Ph-pOH	OCH$_2$PO$_3$Et$_2$	<0.01	2.6	18	285	1912	211	986	ND	ND	1107
H	Ph-pOH	OCH$_2$PO$_3$Et$_2$	0.319	2.1	33	65	272	90	128	198	126	144
OCH$_3$	Ph-pOH	OCH$_2$PO$_3$Et$_2$	0.045	1.8	17	29	146	23	67	106	48	68
OH	Ph-mNH$_2$ /NHEt	OCH$_2$PO$_3$Et$_2$		8.7	67	286	1902	562	789	1781	684	239
H	Ph-mNH$_2$	OCH$_2$PO$_3$Et$_2$	0.126	3.4	39	65	328	16	168	146	74	46
OCH$_3$	Ph-mNH$_2$	OCH$_2$PO$_3$Et$_2$	<0.01	3.6	56	63	535	18	202	117	102	36
OCH$_3$	m-pyridine	OCH$_2$PO$_3$Et$_2$				115	765	106	1019	970	480	352

			Enzymatic assay			Cell-based assay (MT-4) EC$_{50}$/ nM						
R	R1	R2	K_i (nM)	WT IC$_{50}$/ nM	84V90M IC$_{50}$/ nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
H	Ph-mNH$_2$	OCH$_2$PO$_3$Et$_2$	0.126	3.4	39	65	328	16	168	146	74	46
OCH$_3$	Ph-mNH$_2$	OCH$_2$PO$_3$Et$_2$	<0.01	3.6	56	63	535	18	202	117	102	36
OCH$_3$	Ph-mNH$_2$	O(CH$_2$)$_2$PO$_3$Et$_2$										
OCH$_3$	Ph-mNH$_2$	OCONH(CH$_2$)$_2$PO$_3$Et$_2$		11.3	116	74	2265	77	262	214	215	184
OCH$_3$	Ph-mNH$_2$	OCONH(CH$_2$)PO$_3$Et$_2$		9.9	85	58	2151	68	223	203	185	104
H	Ph-pOH	OCH$_2$PO$_3$Et$_2$	0.319	2.1	33	65	272	90	128	222	146	144
OCH$_3$	Ph-pOH	OCH$_2$PO$_3$Et$_2$	0.045	1.8	17	30	148	25	70	129	54	90
OCH$_3$	Ph-pOH	OCONH(CH$_2$)$_2$PO$_3$Et$_2$		6.6	49	33	495	31	74	51	55	223
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
H	Ph	OCH$_2$PO$_3$Et$_2$	0.656	3.9	48	107	2456	293	1438	1899	3292	589
H	Ph	OH	0.330	15	162	1261	>6000	2952	>6000			
H	Ph	OCH$_2$PO$_3$Bn$_2$	0.125	7.4	158	1769	>6000	3135	>6000			
H	Ph	OCH$_2$PO$_3$H$_2$	0.386	9.7	210	>600	>600	ND	ND			

						0	0					
H	Ph	Mono-lac-Et	0.120	6.6	56	1726	>600 0	2793	>6000			
H	Ph	Mono-Ala-Et		5	50	310	2943	238	2851	1948	2450	1250

		Enzymatic assay			Cell-based assay (MT-4) EC$_{50}$/ nM						
R1	R2	K_i (nM)	WT IC$_{50}$/ nM	84V 90M IC$_{50}$/ nM	WT	84V 90M	30N 82I88 D	48V 54V 82A	48V54 V82S	48V82 A90M	4615 0V
Phenyl		0.03	3.0	9.1	165	819	82	82	73	45	88
Phenyl		0.42	6.6	85	1226	>600	869	774	ND	ND	937
Phenyl		0.37	5.8	43.3	193	2312	281	705	ND	ND	772
Phenyl			109	>25	>6000	ND	ND	ND	ND	ND	ND
Phenyl											
Phenyl											
Phenyl											
Bn-O		1.43	302	114	>6000	>600	ND	ND	ND	ND	ND
Bn-O		>5	>25	ND	5949	ND	ND	ND	ND	ND	ND
H-O		>5	130	348	2006	3121	ND	ND	ND	ND	ND

All publications and patent applications cited herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the claims of the invention.

In the following claims, the subscript and superscripts of a given variable are distinct. For example, R_1 is distinct from R^1.

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1.   An HIV protease inhibitor compound comprising a phosphonate group.

2.   An HIV protease inhibitor compound of claim 1 selected from:

a Saquinavir-like phosphonate protease inhibitor compound,

a Lopinavir-like phosphonate protease inhibitor compound,

a Ritonavir-like phosphonate protease inhibitor compound,

10   a Indinavir-like phosphonate protease inhibitor compound,

a Atazanavir-like phosphonate protease inhibitor compound,

a Nelfinavir-like phosphonate protease inhibitor compound,

a Tipranavir-like phosphonate protease inhibitor compound,

a Amprenavir-like phosphonate protease inhibitor compound,

15   a KNI-like phosphonate protease inhibitor compound, and

a Cyclic Carbonyl-like phosphonate protease inhibitor compound;

and pharmaceutically acceptable salts, hydrates, and formulations thereof.

3.   A compound selected from the Formulas:

I   II   X = C, SO

III   IV

V   VI

Va

VII

VIIIa   VIIIb

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VIIIc   and   VIIId;
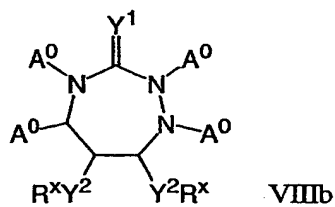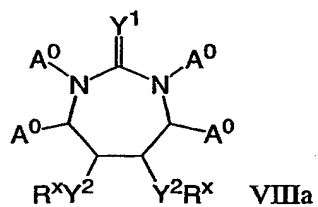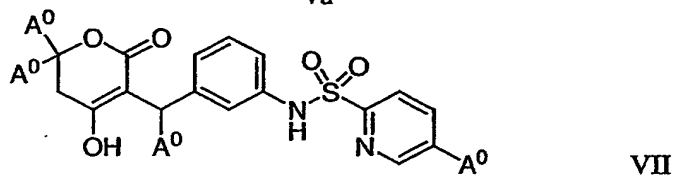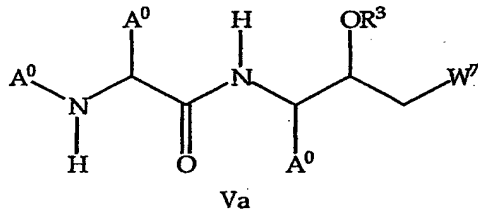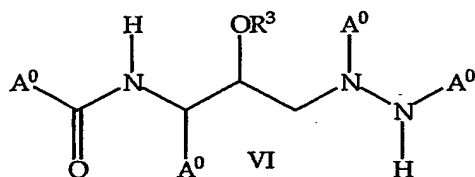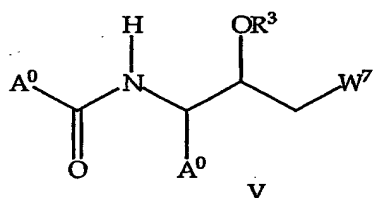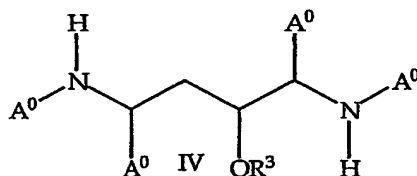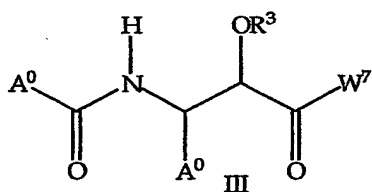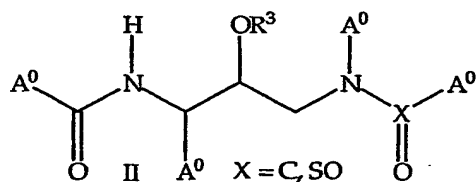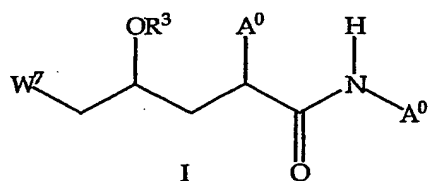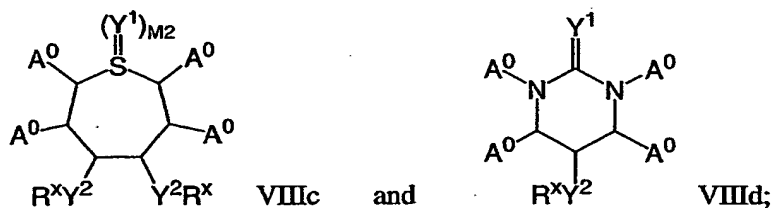
wherein:

A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1;

5   A^1 is:
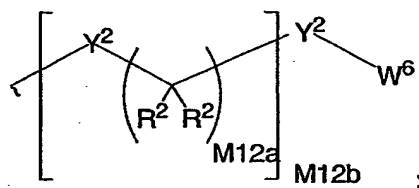
A^2 is:
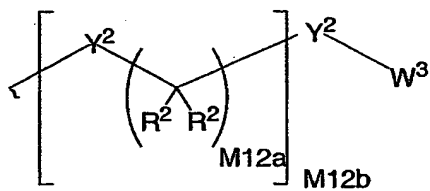
10   A^3 is:
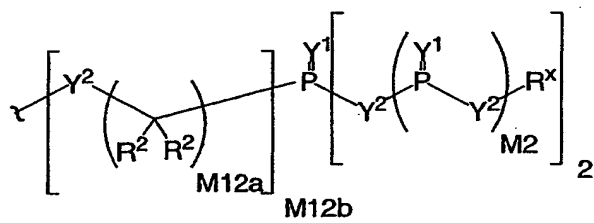
Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

15   R^x is independently H, R^1, W^3, a protecting group, or the formula:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups, or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2 A^0 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

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M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

4.   A compound of claim 3 selected from:

, and

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5.   A compound of claim 3 selected from:
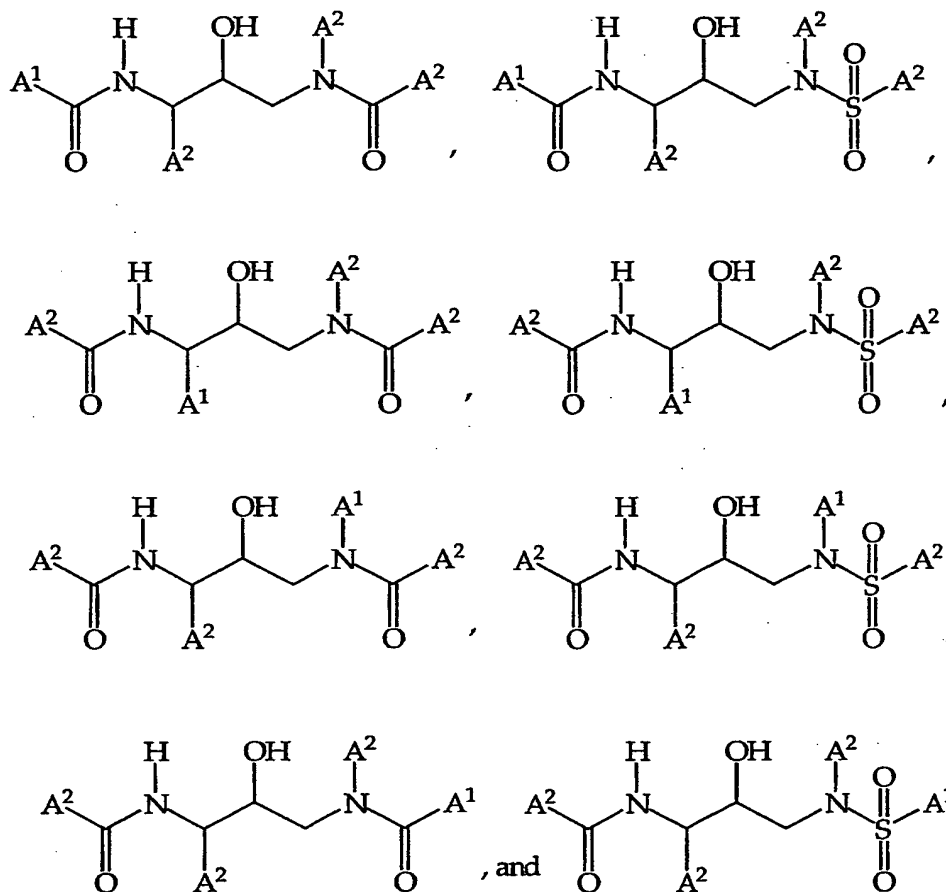
6.   A compound of claim 3 selected from:

5

, and

7.   A compound of claim 3 selected from:

and
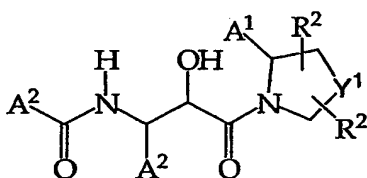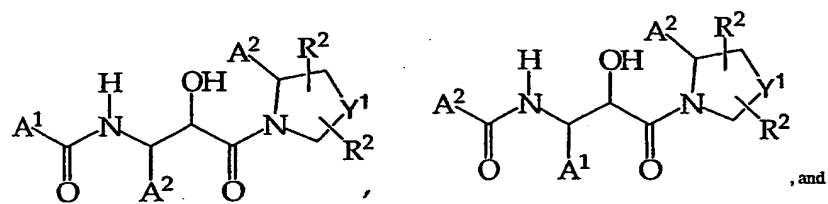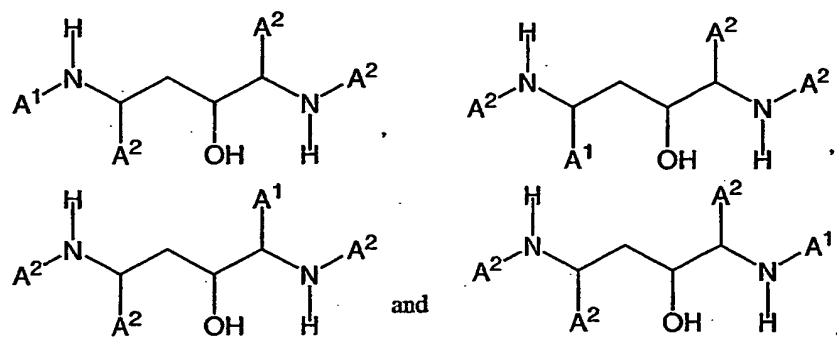
5   8.   A compound of claim 3 selected from:

,

,

,

and

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9.   A compound of claim 3 selected from:

,
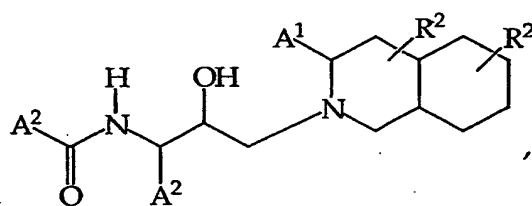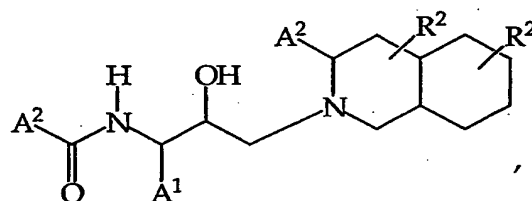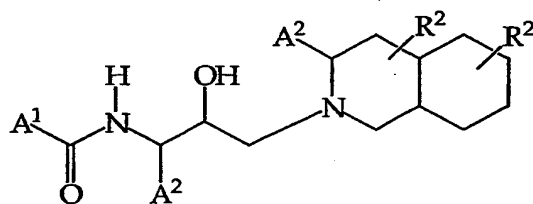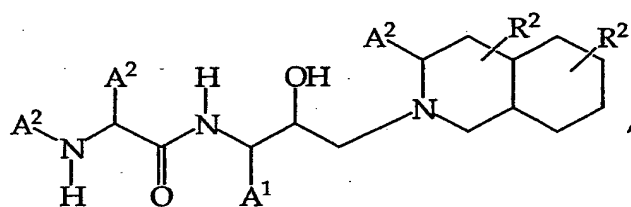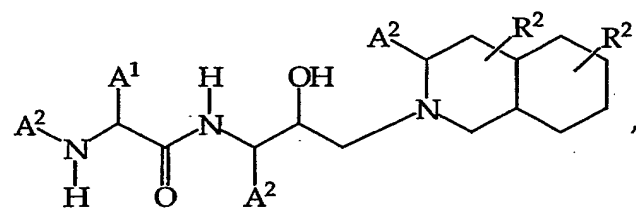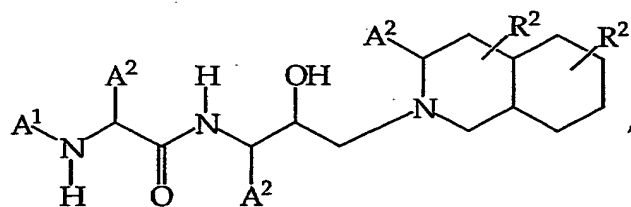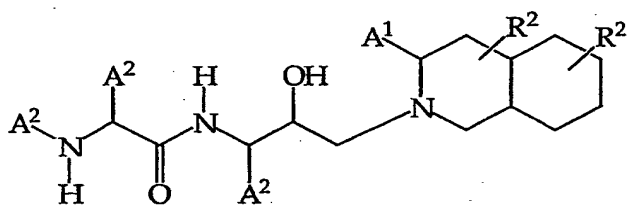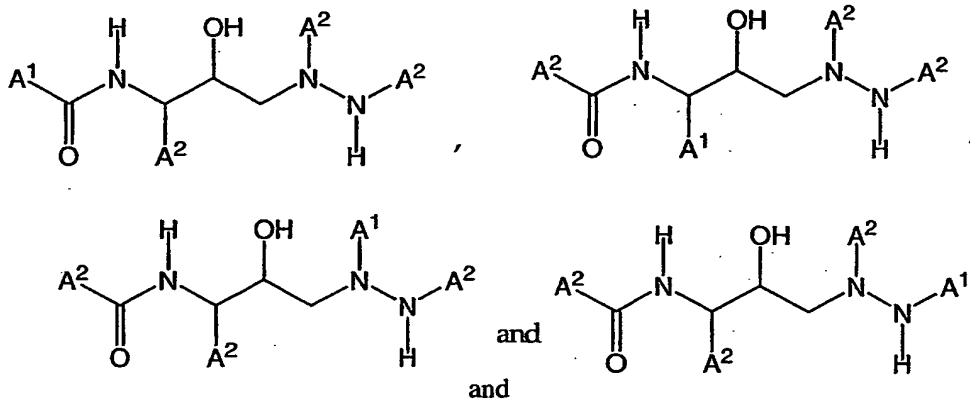
10.   A compound of claim 3 selected from:

and
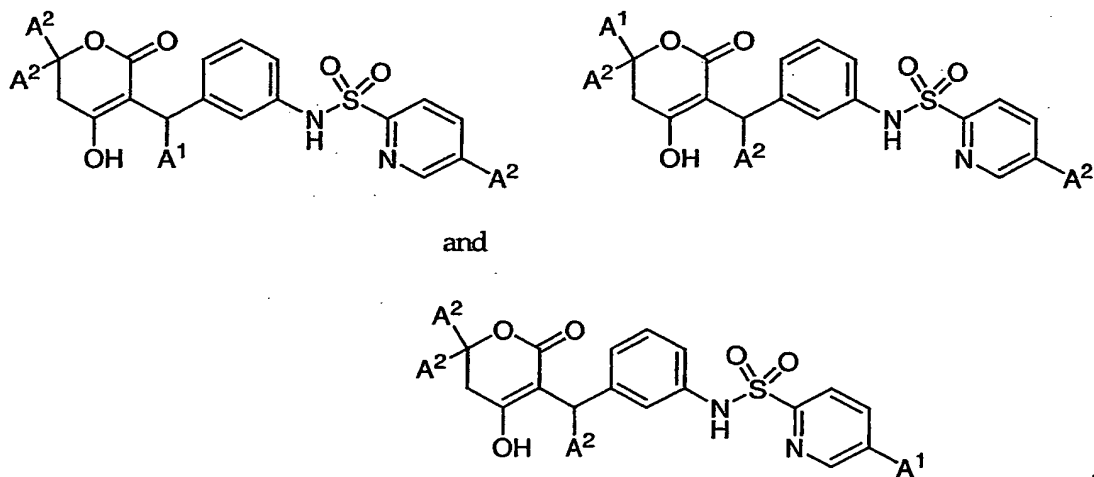
11.   A compound of claim 3 selected from:
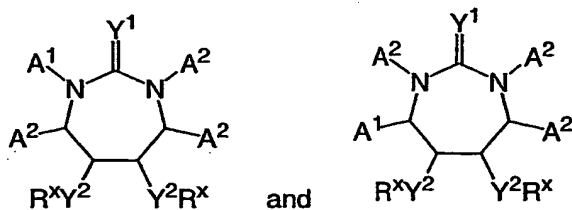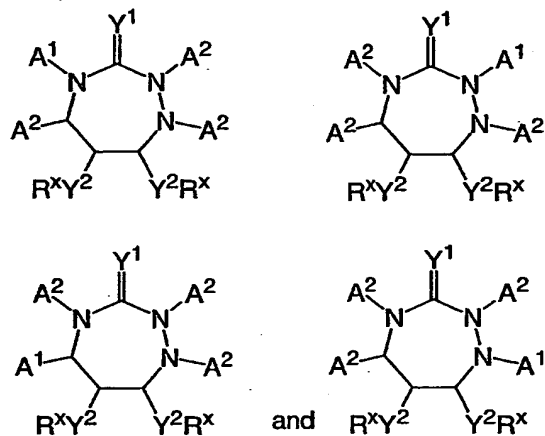
and

12.   A compound of claim 3 selected from:

and

13.   A compound of claim 3 selected from:

and

14.   A compound of claim 3 selected from:

and
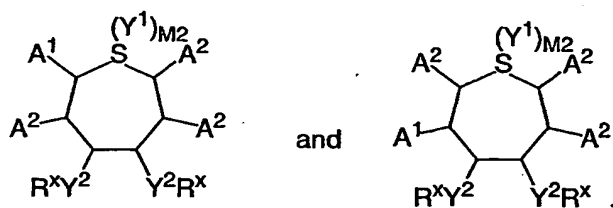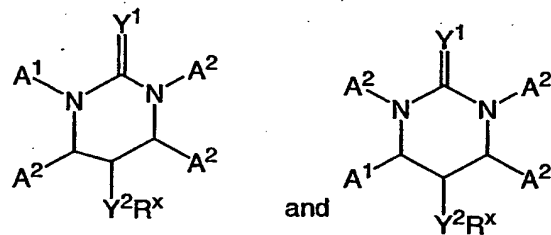
15.   A compound of claim 3 wherein A^1 is of the formula:
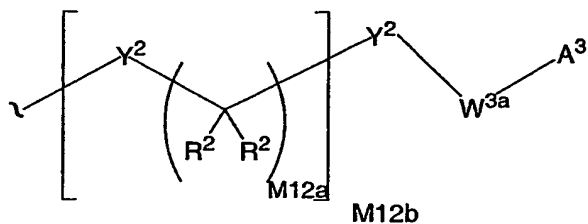
16.   A compound of claim 15 wherein A^1 is of the formula:
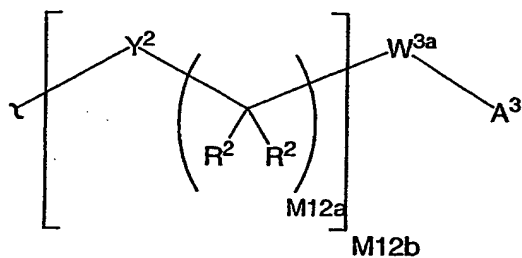
17.   A compound of claim 16 wherein A^1 is of the formula:
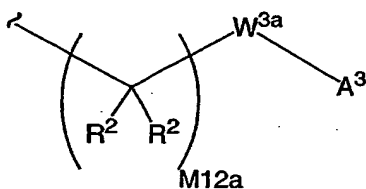
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18.   A compound of claim 17 wherein A^1 is of the formula:
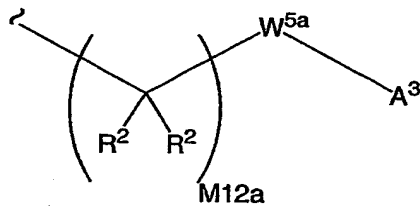
10   and W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with
0 or 1 R^2 groups.

19.   A compound of claim 18 wherein M12a is 1.

20.   A compound of claim 3 wherein A^3 is of the formula:

M12b
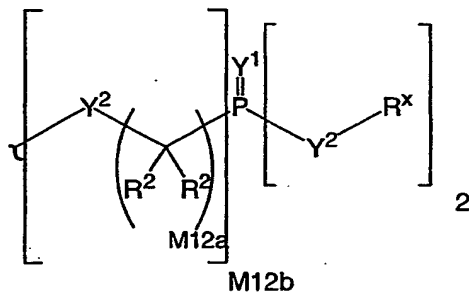
21.   A compound of claim 20 wherein A^3 is of the formula:
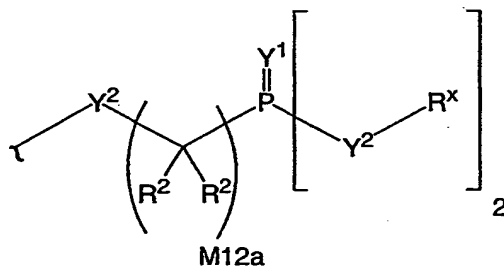
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22.   The compound of claim 21 wherein A^3 is of the formula:
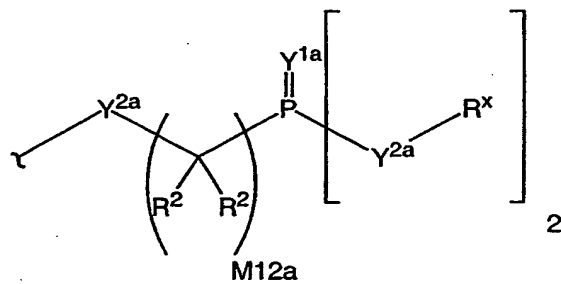
Y^{1a} is O or S; and

10   Y^{2a} is O, $N(R^x)$ or S.

23.   The compound of claim 22 wherein A^3 is of the formula:

M12a
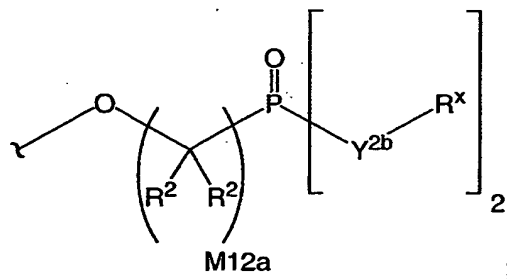
and Y^{2b} is O or $N(R^x)$.

5   24.   The compound of claim 23 wherein A^3 is of the formula:
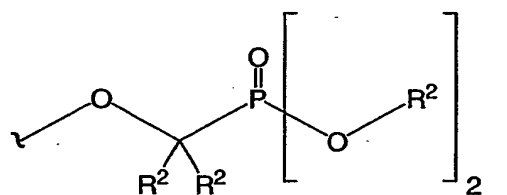
25.   The compound of claim 23 wherein A^3 is of the formula:
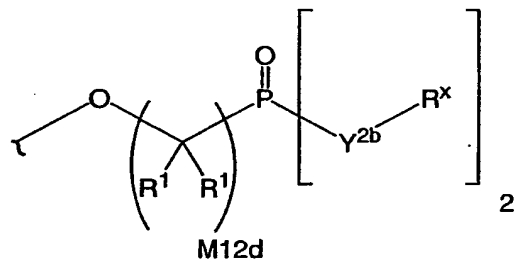
M12d

10   R^1 is independently H or alkyl of 1 to 18 carbon atoms;

Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

26.   The compound of claim 25 wherein A^3 is of the formula:
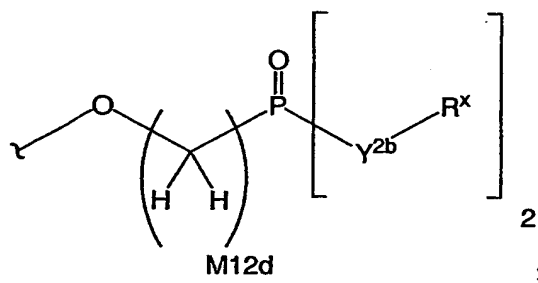
Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

5

27.   The compound of claim 26 wherein M12d is 1.

28.   The compound of claim 3 wherein A^3 is of the formula:
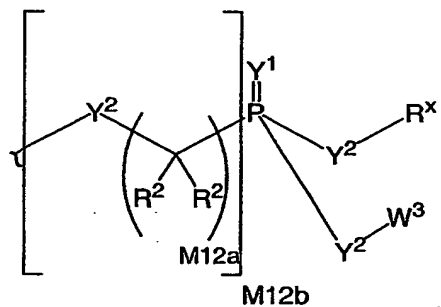
29.   The compound of claim 28 wherein A³ is of the formula:
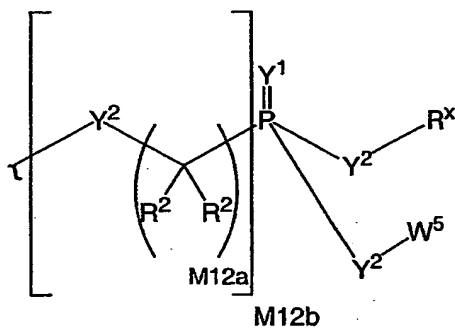
5   30.   The compound of claim 29 wherein W⁵ is a carbocycle.

31.   The compound of claim 30 wherein A³ is of the formula:
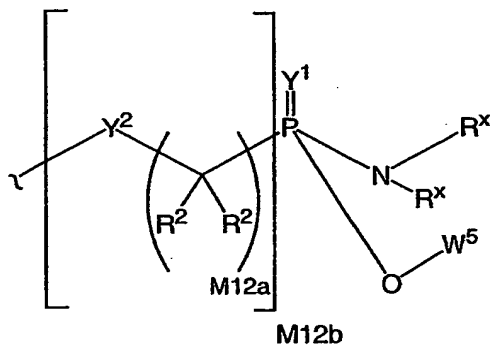
10   32.   The compound of claim 31 wherein W⁵ is phenyl.

33.   The compound of claim 28 wherein M12b is 1.

34.   The compound of claim 33 wherein A^3 is of the formula:
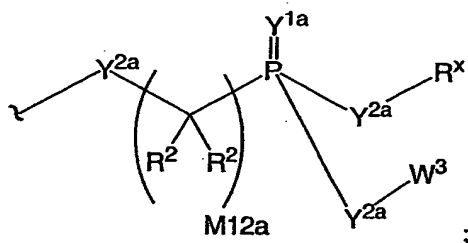
Y^{1a} is O or S; and

Y^{2a} is O, $N(R^x)$ or S.

35.   The compound of claim 34 wherein A^3 is of the formula:
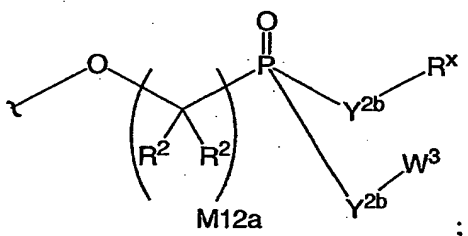
and Y^{2b} is O or $N(R^x)$.

36.   The compound of claim 35 wherein A^3 is of the formula:
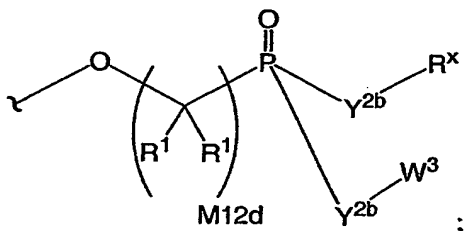
R^1 is independently H or alkyl of 1 to 18 carbon atoms;

Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

37.   The compound of claim 36 wherein R^1 is H.

38.   The compound of claim 36 wherein M12d is 1.

39. The compound of claim 36 wherein A^3 is of the formula:
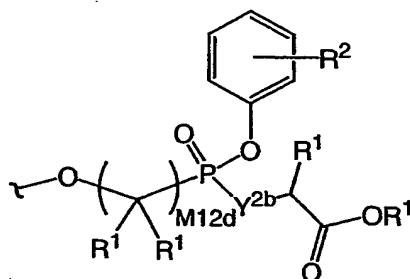
wherein the phenyl carbocycle is substituted with 0 to 3 R^2 groups.

5

40. The compound of claim 39 wherein A^3 is of the formula:
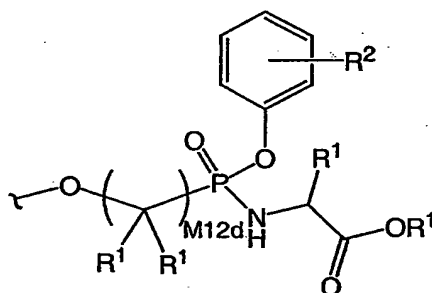
41. The compound of claim 40 wherein A^3 is of the formula:
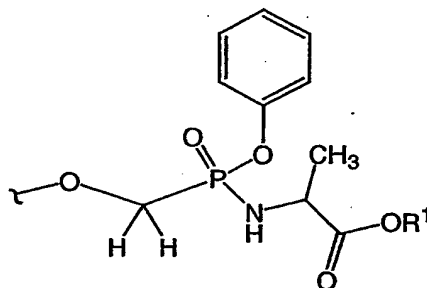
42.   A compound of claim 3 wherein R^x is of the formula:
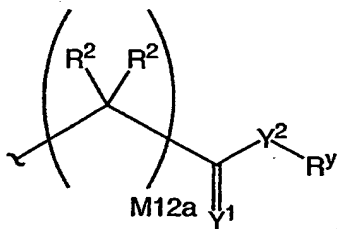
43.   A compound of claim 42 wherein R^x is of the formula:
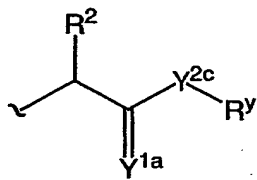
5

Y^{1a} is O or S; and

Y^{2c} is O, N(R^y) or S.

44.   A compound of claim 43 wherein R^x is of the formula:
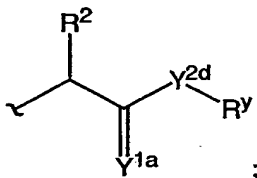
10

Y^{1a} is O or S; and

Y^{2d} is O or N(R^y).
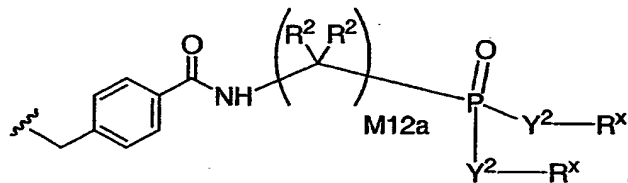
45.   A compound of claim 44 wherein R^x is of the formula:
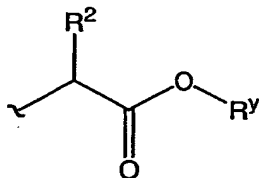
15

46.   A compound of claim 45 wherein R^x is of the formula:
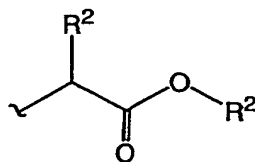
47.   The compound of claim 3 wherein R^x is of the formula:

M12a
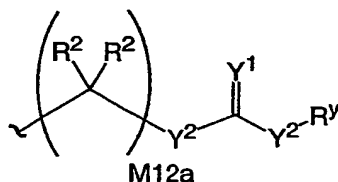
48.   The compound of claim 47 wherein A^3 is of the formula:
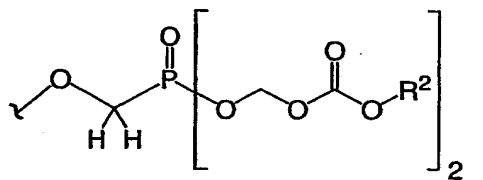
49.   The compound of claim 3 wherein A^3 is of the formula:

M12a   ; and

R^x is of the formula:

M12a

-1667-
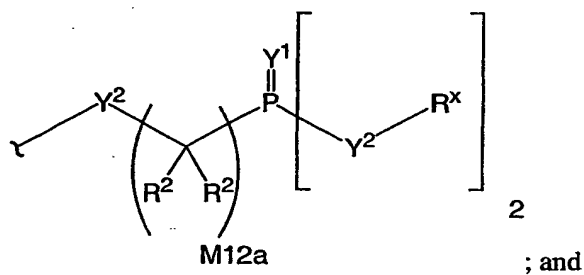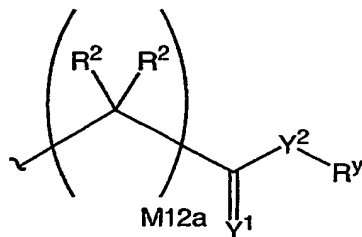
50.   The compound of claim 49 wherein A^3 is of the formula:
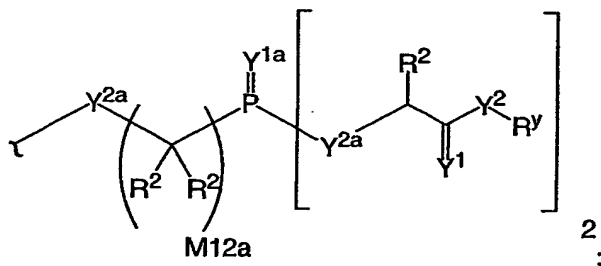
Y^{1a} is O or S; and

Y^{2a} is O, N(R^2) or S.

51.   The compound of claim 50 wherein A^3 is of the formula:
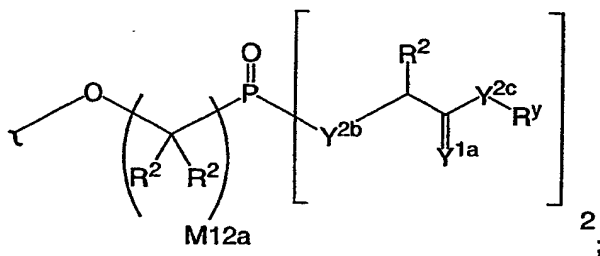
Y^{1a} is O or S;

Y^{2b} is O or N(R^2); and

Y^{2c} is O, N(R^y) or S.

52.   The compound of claim 51 wherein A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or N(R^2);

-1668-
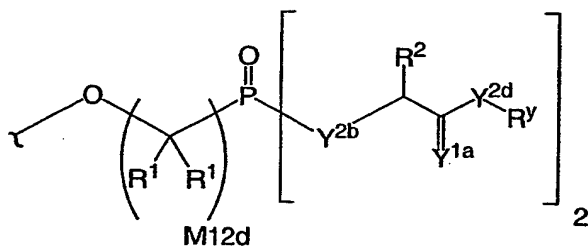
Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

53.   The compound of claim 52 wherein A^3 is of the formula:
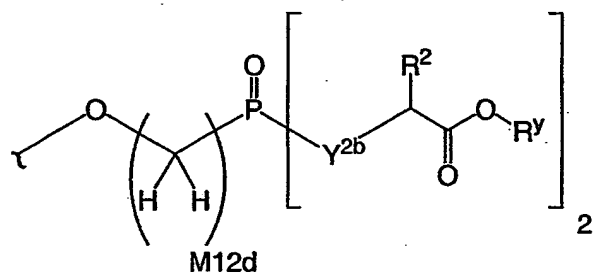
Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

54.   The compound of claim 53 wherein A^3 is of the formula:
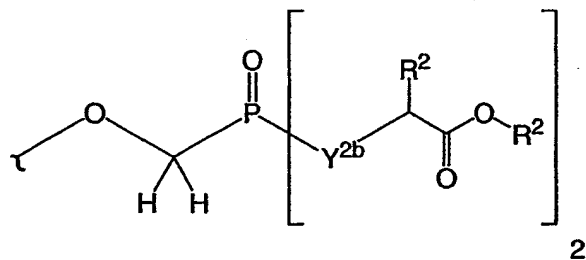
and Y^{2b} is O or $N(R^2)$.

55.   The compound of claim 54 wherein A^3 is of the formula:
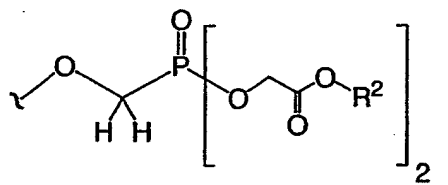
56.   .   The compound of claim 3 wherein A^3 is of the formula:

;
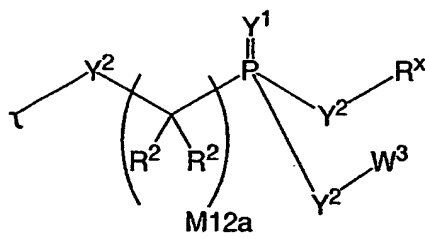
R^x is of the formula:

.
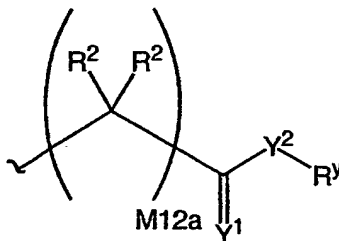
5

57.   The compound of claim 56 wherein A^3 is of the formula:

;
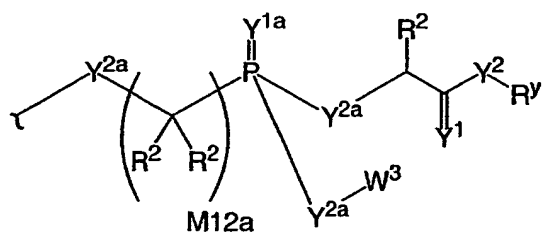
Y^{1a} is O or S; and

10   Y^{2a} is O, $N(R^2)$ or S.

58.   The compound of claim 57 wherein A^3 is of the formula:

;
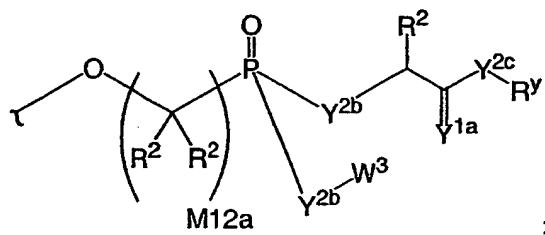
15   Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

-1670-

Y^{2c} is O, N(R^y) or S.

59.   The compound of claim 58 wherein A^3 is of the formula:
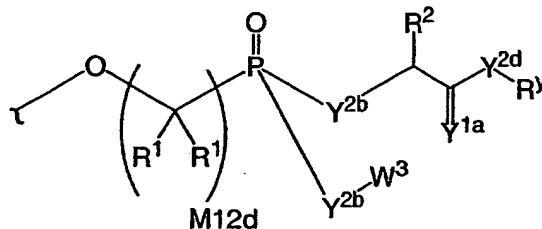
R^1 is independently H or alkyl of 1 to 18 carbon atoms;

Y^{1a} is O or S;

Y^{2b} is O or N(R^2);

Y^{2d} is O or N(R^y); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

60.   The compound of claim 59 wherein A^3 is of the formula:
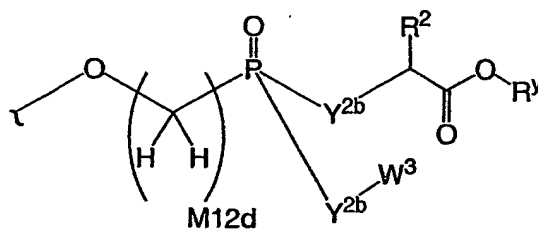
Y^{2b} is O or N(R^2); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

61. The compound of claim 60 wherein A^3 is of the formula:
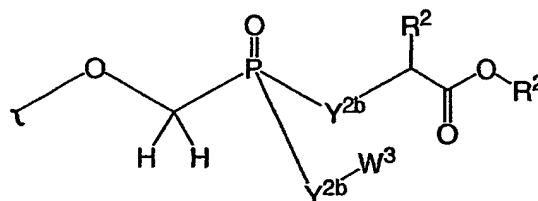
and Y^{2b} is O or N(R^2).

62.   The compound of claim 3 wherein A^1 is of the formula:

$$\left[\ \ Y^2 \ \left(\underset{R^2 \ R^2}{}\right)_{M12a} Y^2 - W^6 - A^3 \right]_{M12b} ; \text{ and}$$

A^3 is of the formula:

$$\left[\ \ Y^2 \ \left(\underset{R^2 \ R^2}{}\right)_{M12a} \overset{\overset{Y^1}{\|}}{P}\ \left[Y^2 - R^x \right] \right]_{M12b} {}_2$$
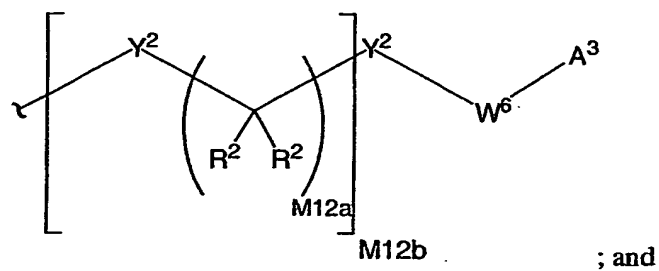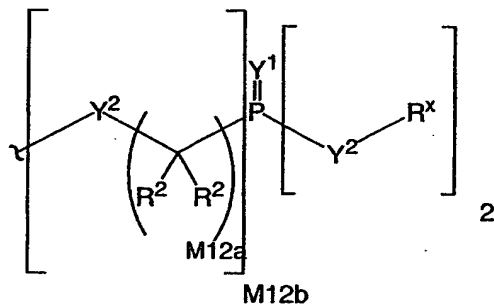
63.   The compound of claim 62 wherein A^1 is of the formula:

$$\left[\ \ Y^2 \ \left(\underset{R^2 \ R^2}{}\right)_{M12a} W^6 - A^3 \right]_{M12b} ;$$

A^3 is of the formula:

$$\left[\ \ Y^2 \ \left(\underset{R^2 \ R^2}{}\right)_{M12a} \overset{\overset{Y^1}{\|}}{P}\ \left[Y^2 - R^x \right] \right]_2 ; \text{ and}$$

R^x is of the formula:

-1672-
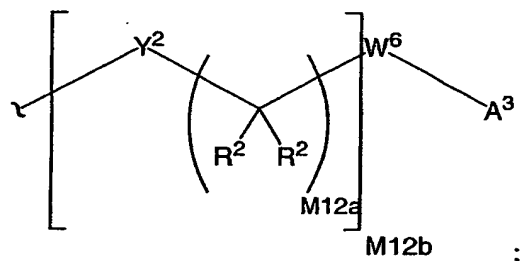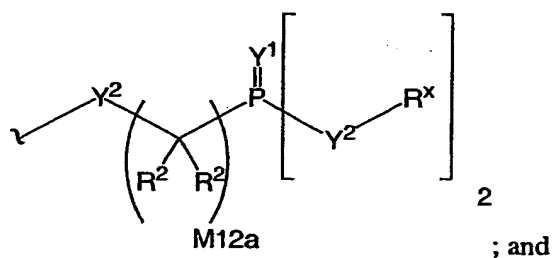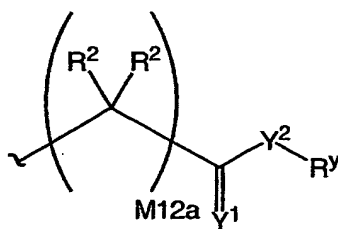
64.   The compound of claim 63 wherein A^1 is of the formula:
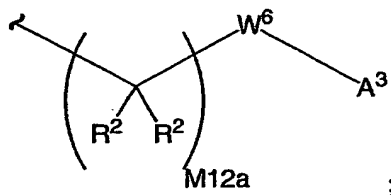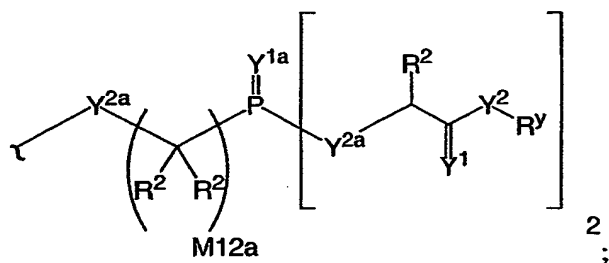
A^3 is of the formula:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

65.   The compound of claim 64 wherein A^1 is of the formula:
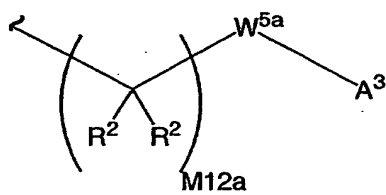
W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;
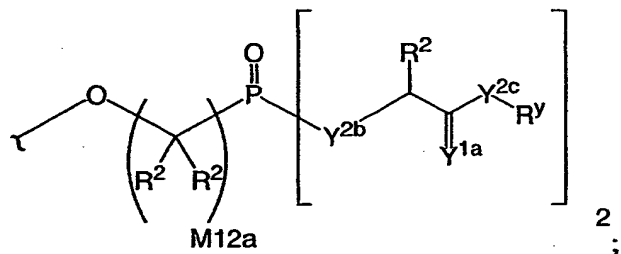
A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

66.   The compound of claim 65 wherein A^1 is of the formula:
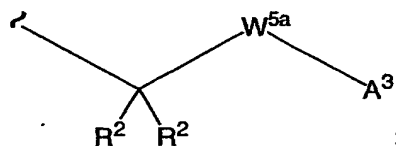
W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;
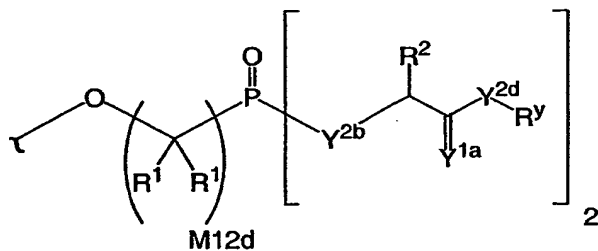
A^3 is of the formula:

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

67.   The compound of claim 66 wherein A^1 is of the formula:
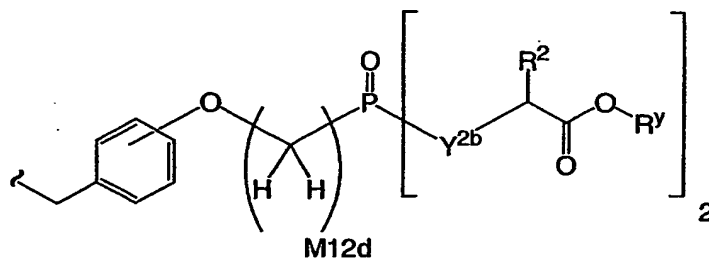
M12d

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

68.   The compound of claim 66 wherein A^1 is of the formula:
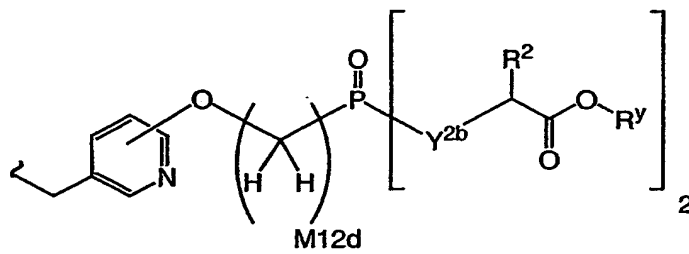
M12d

and Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

69.   The compound of claim 3 wherein A^1 is of the formula:

; and
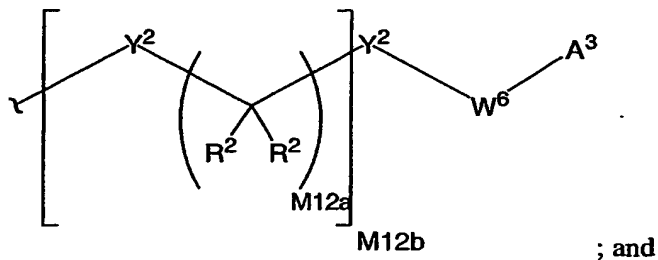
A^3 is of the formula:
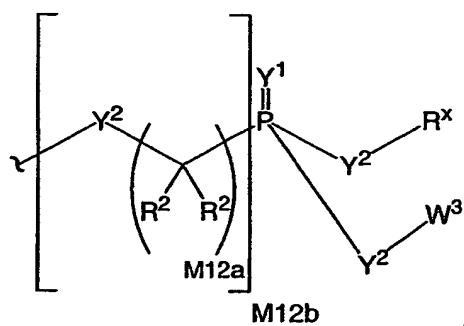
70.   The compound of claim 69 wherein A^1 is of the formula:
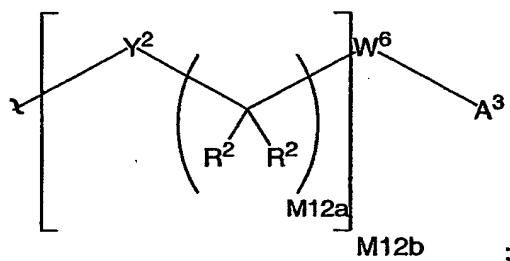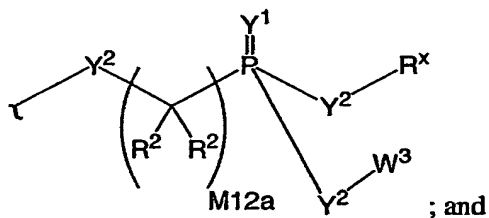
A^3 is of the formula:
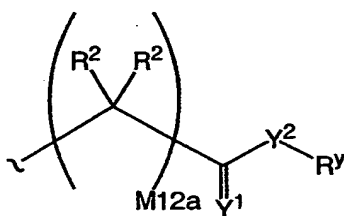
R^x is of the formula:

71.   The compound of claim 70 wherein A^1 is of the formula:
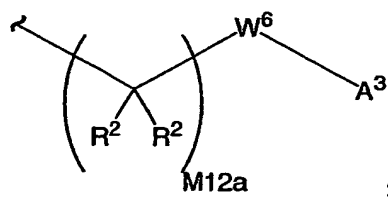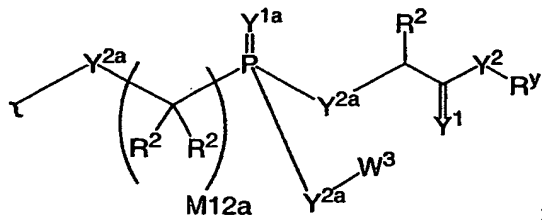
A^3 is of the formula:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

72.   The compound of claim 71 wherein A^1 is of the formula:
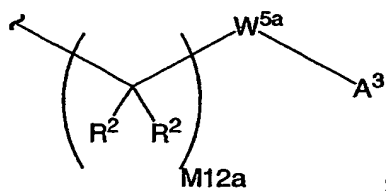
W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

-1677-
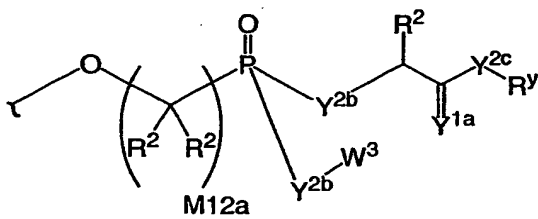
73.   The compound of claim 72 wherein A^3 is of the formula:
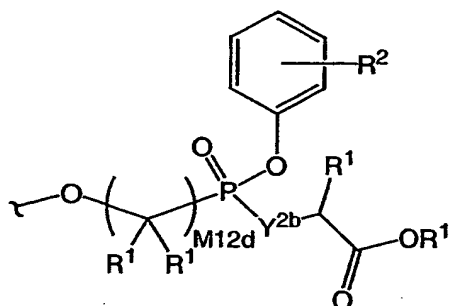
wherein R^1 is independently H or alkyl of 1 to 18 carbon atoms; and the phenyl
carbocycle is substituted with 0 to 3 R^2 groups.

74.   The compound of claim 70 wherein A^1 is of the formula:
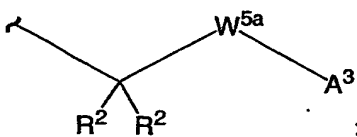
W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1
R^2 groups;
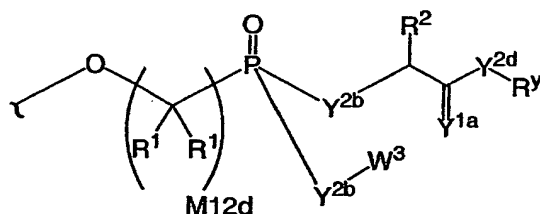
A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

75.   A compound of claim 74 wherein Y^{2b} is O and W^3 is phenyl.

76.   A compound of claim 75 wherein A^3 is of the formula:

-1678-
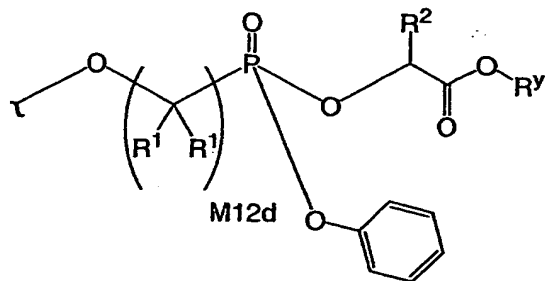
77.   A compound of claim 75 wherein A³ is of the formula:
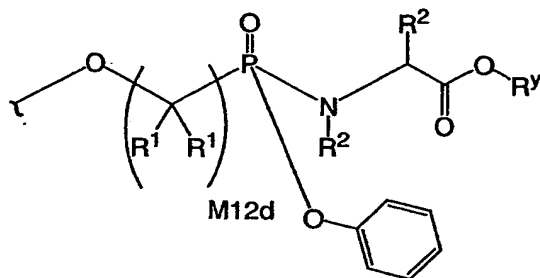
5

78.   A compound of claim 74 wherein A¹ is of the formula:
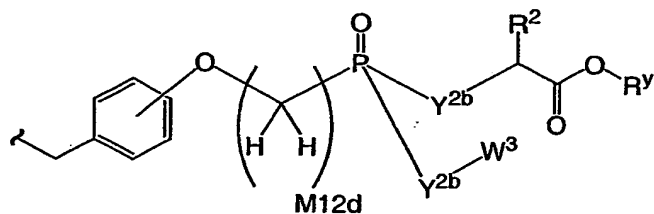
Y^{2b} is O or $N(R^2)$; and

10   M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

79.   The compound of claim 3 wherein A^2 is of the formula:
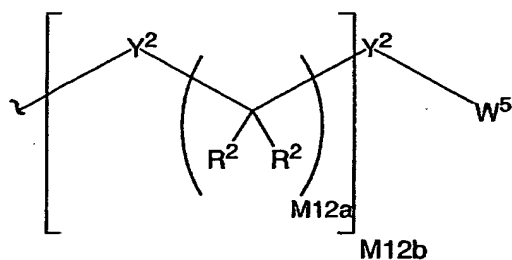
80.   The compound of claim 79 wherein A^2 is of the formula:
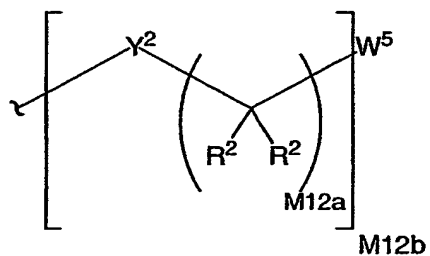
81.   The compound of claim 80 wherein M12b is 1.

82.   The compound of claim 80 where M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

83.   The compound of claim 80 wherein A^2 is of the formula:
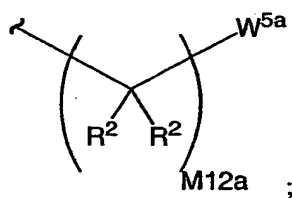
and W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

84.   The compound of claim 83 wherein M12a is 1.

85.   The compound of claim 83 wherein A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

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86.   The compound of claim 3 wherein A^2 is of the formula:
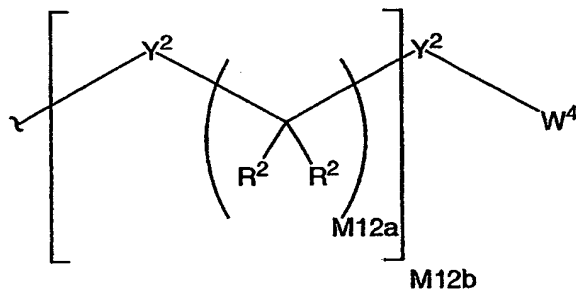
87.   The compound of claim 86 wherein A^2 is of the formula:
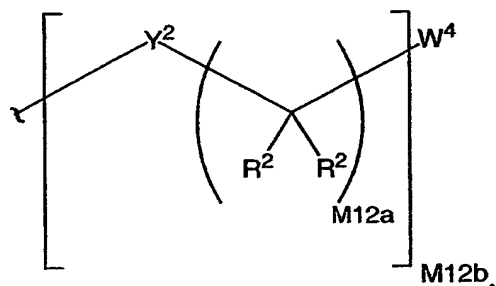
10

88.   The compound of claim 87 wherein M12b is 1.

89.   A Formula II compound of claim 5 having the formula:
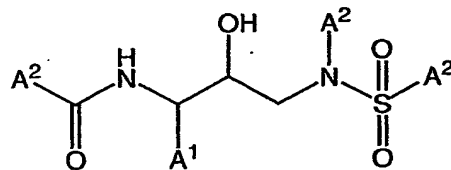
15

90.   A compound of claim 89 having the formula:
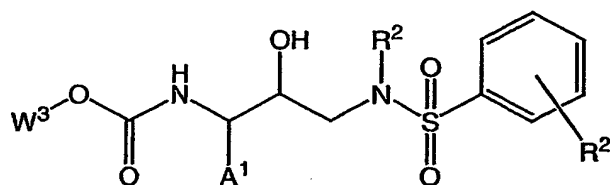
91.   A compound of claim 90 having the formula:
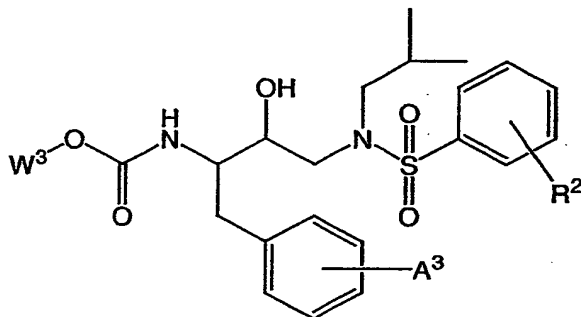
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92.   A compound of the formula MBF.

93.   A compound of claim 92 having the formula:

10
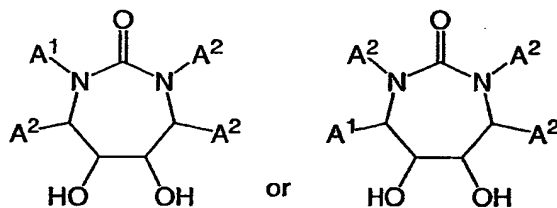
94.   The compound of claim 93 wherein A^2 is selected from benzyl, substituted benzyl, heterocycle and substituted heterocycle.

-1682-

95.   A compound of claim 3 wherein A^1 is of the formula:
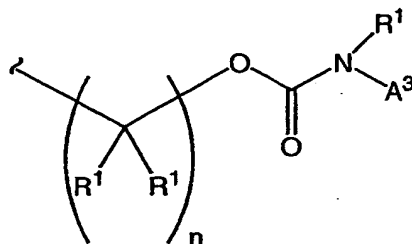
R^1 is independently H or alkyl of 1 to 18 carbon atoms; and n is an integer from 1 to 18; A^3 is of the formula:
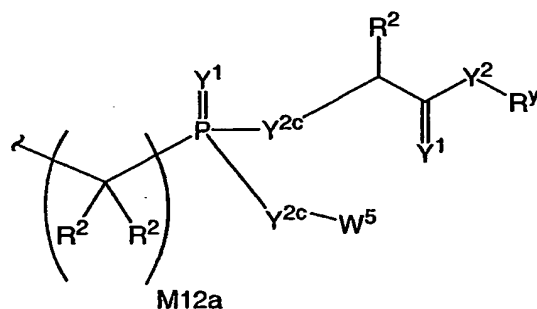
and Y^{2c} is O, $N(R^y)$ or S.

96.   The compound of claim 95 wherein R^1 is H and n is 1.

97.   A compound of claim 91 having the formula:
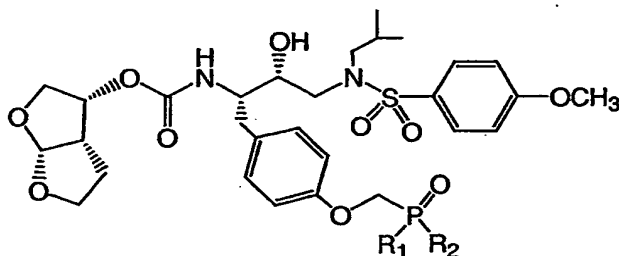
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

98. A compound of claim 91 having the formula:
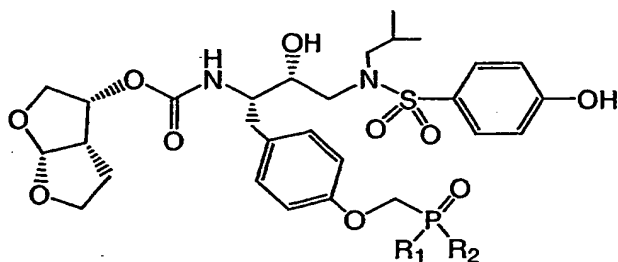
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

99. A compound of claim 91 having the formula:
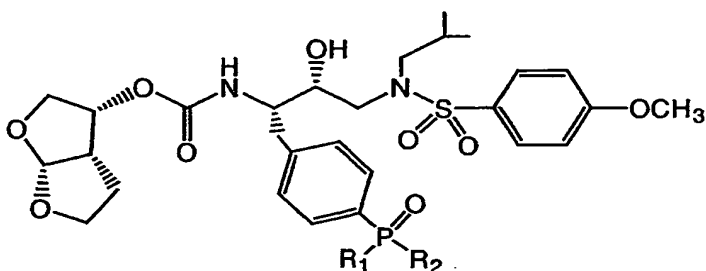
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

100. A compound of claim 91 having the formula:
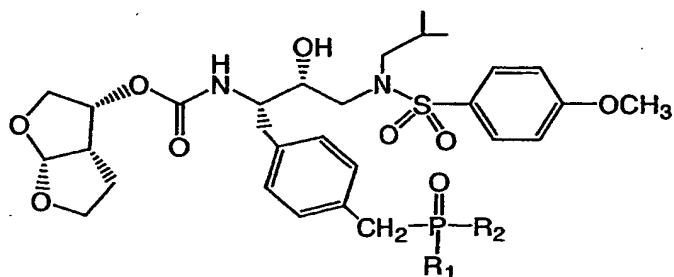
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

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101.   A compound of claim 91 having the formula:
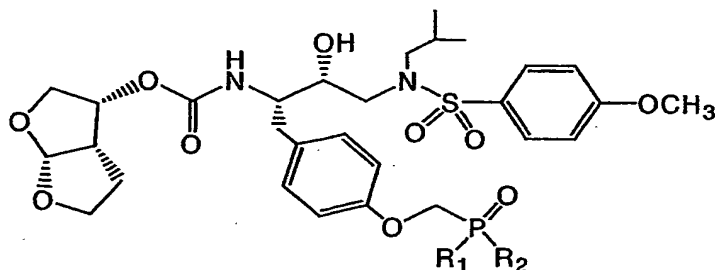
wherein R_1 and R_2 are independently selected from $-NR$ where R is C_1-C_6 alkyl or an
amino acid ester.

102.   The compound of claim 101 wherein R_1 and R_2 are independently selected
from $-NMe$, $-NEt$, Gly-Et, Ala-Et, Aba-Et, Val-Et, Leu-Et, Phe-Bu, and Phe-Et.

103.   A compound of claim 91 having the formula:
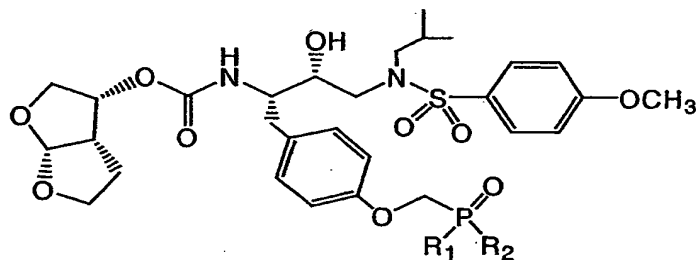
or
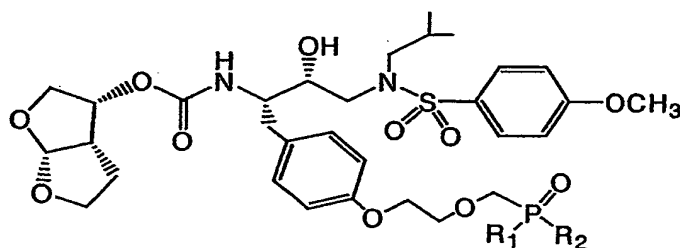
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy,
trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, and a lactate ester.

104.   The compound of claim 103 wherein R₁ is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and R₂ is Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et, Lac-Bn, Lac-Bn, Lac-OH, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, or DiMePro-Me.

5

105.   A compound of claim 104 where the lactate ester is the (R) configuration.

106.   A compound of claim 104 where the lactate ester is the (S) configuration.

10   107.   A compound of claim 91 having the formula:
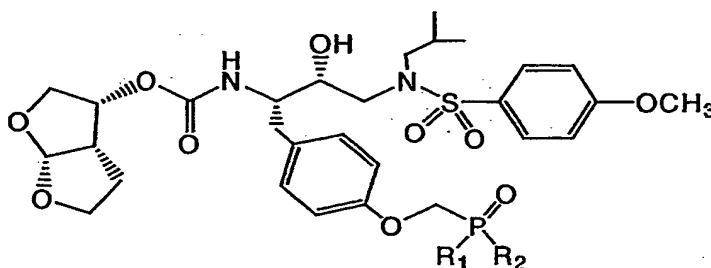
wherein R₁ is phenoxy, benzyloxy, ethoxy, trifluoroethoxy, or hydroxyl; and R₂ is an amino acid ester.

15

108.   The compound of claim 107 wherein the amino acid ester is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et, Aba-Bu, and Ala-OH.

109.   A compound of claim 91 having the formula:
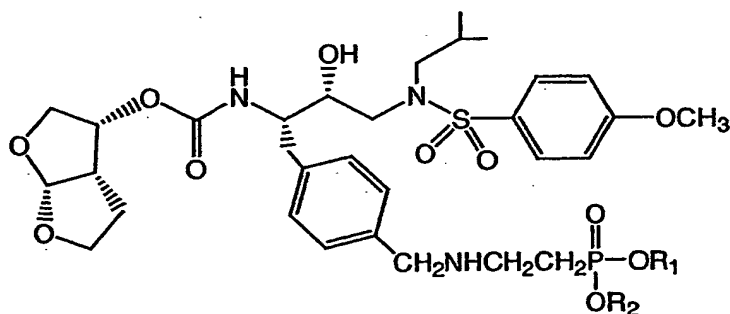
wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy,
trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, an amino acid ester
and a lactate ester.

110.   The compound of claim 109 wherein R_1 is hydroxy, methoxy, ethoxy,
trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and R_2 is a lactate
ester selected from Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et,
Lac-Bn, Lac-Bn, Lac-OH, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, and DiMePro-
Me.

111.   The compound of claim 109 wherein R_1 is hydroxy, methoxy, ethoxy,
trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and R_2 is an amino
acid ester is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et,
Aba-Bu, and Ala-OH.

112.   A compound of claim 5 having the formula:
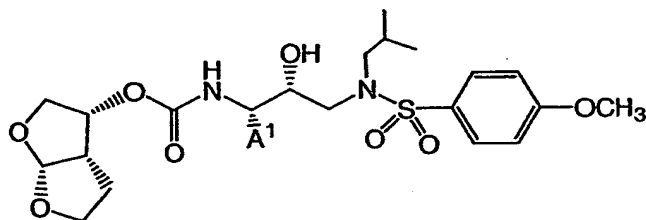
wherein A^1 is selected from the formulas:
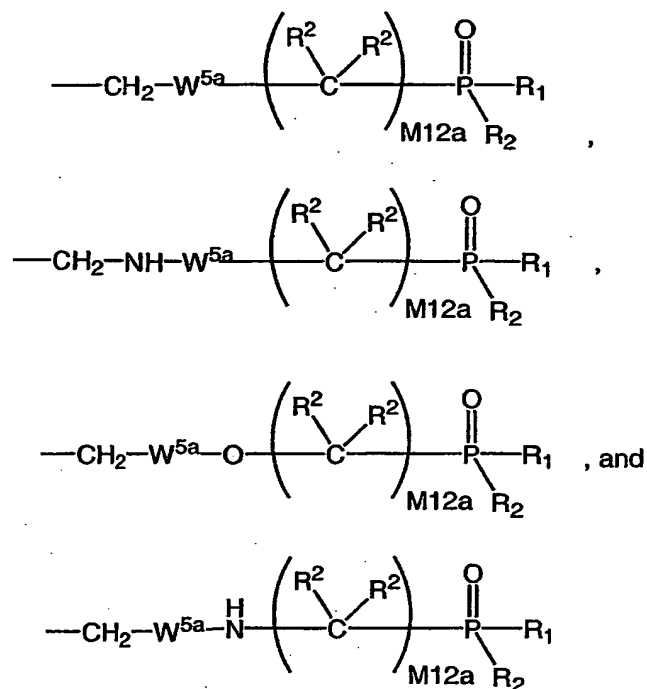
$$—CH_2—W^{5a}\left(\underset{\overset{|}{C}}{\overset{R^2\quad R^2}{}}\right)_{M12a}\overset{\overset{O}{\|}}{\underset{R_2}{P}}—R_1 \quad ,$$

$$—CH_2—NH—W^{5a}\left(\underset{\overset{|}{C}}{\overset{R^2\quad R^2}{}}\right)_{M12a}\overset{\overset{O}{\|}}{\underset{R_2}{P}}—R_1 \quad ,$$

$$—CH_2—W^{5a}—O\left(\underset{\overset{|}{C}}{\overset{R^2\quad R^2}{}}\right)_{M12a}\overset{\overset{O}{\|}}{\underset{R_2}{P}}—R_1 \quad , \text{ and}$$

$$—CH_2—W^{5a}—\overset{H}{N}\left(\underset{\overset{|}{C}}{\overset{R^2\quad R^2}{}}\right)_{M12a}\overset{\overset{O}{\|}}{\underset{R_2}{P}}—R_1$$

R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, an amino acid ester and a lactate ester; and

5   W^{5a} is selected from the formulas:

, and
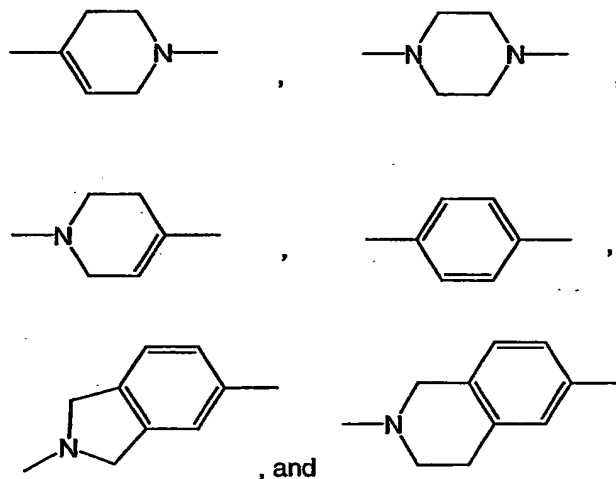
113.   A compound of claim 112 wherein A^1 is selected from the formulas:
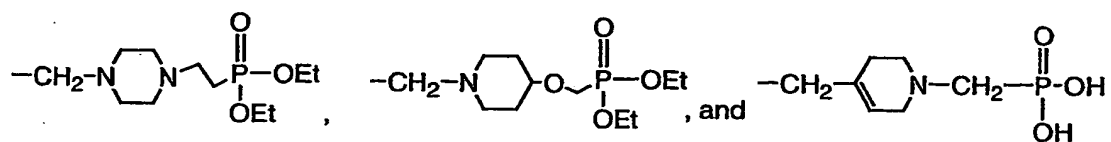
114. A compound of claim 94 having the structure:
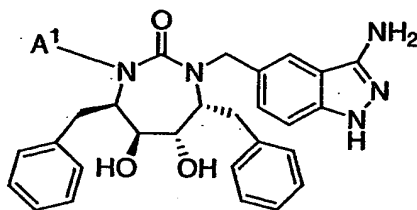
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115. A compound of claim 114 having the structure:
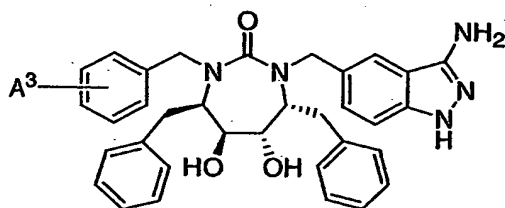
wherein the ortho, meta, or para carbon of the phenyl ring is substituted with A^3.

116.   A compound of claim 115 wherein A³ is of the formula:

M12a
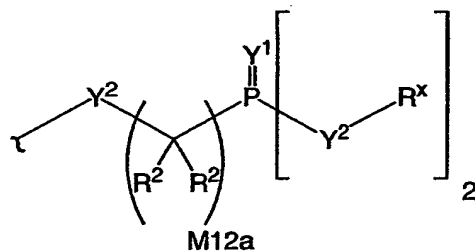
117.   A compound of claim 115 wherein A³ is of the formula:

5

M12b
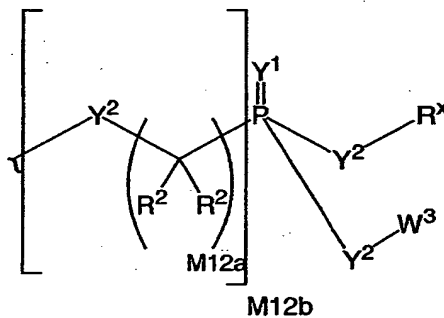
118.   A compound of claim 114 wherein A¹ is of the formula:

10

119.   A compound of claim 118 wherein Y² is O, R² is H, and Rˣ is C₁–C₆ alkyl.

120.   A compound of claim 118 wherein A^1 is of the formula:

;
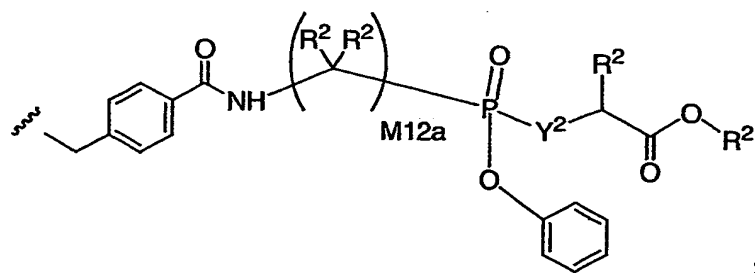
and Y^2 is O, NH, or NR^4.

5   121.   A Formula VIIIa compound of claim 3 having the structure:
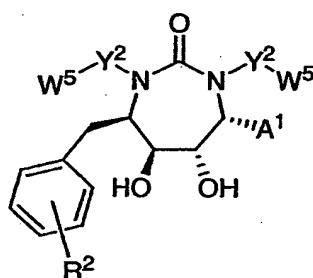
122.   A Formula VIIIa compound of claim 3 having the structure:

10

123.   A compound selected from the Formulas:

I

II   X = C, SO

III

IV

V

VI

VII

5

VIIIa

VIIIb

VIIIc   and

VIIId;

10

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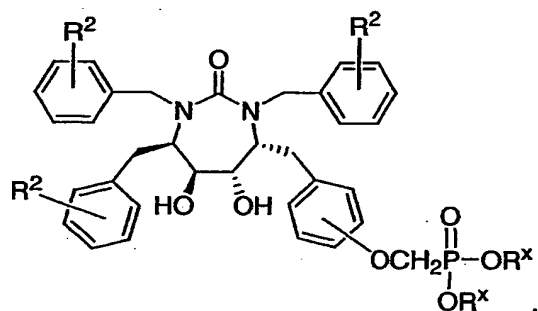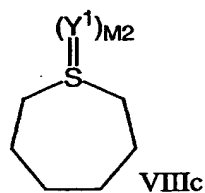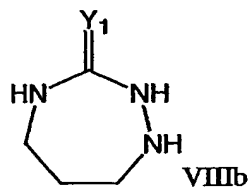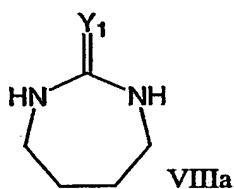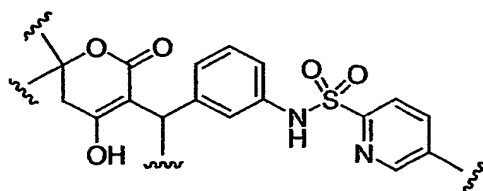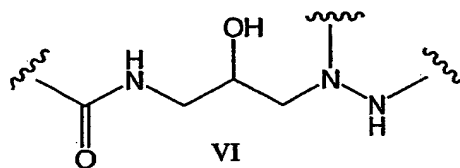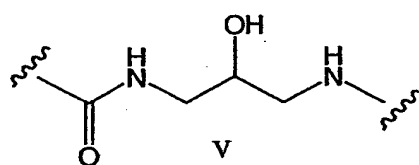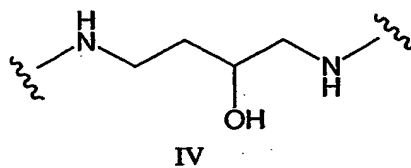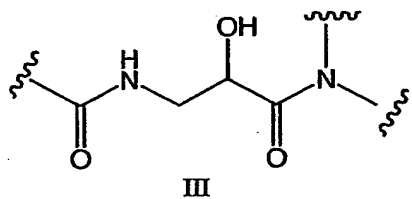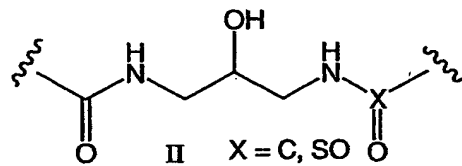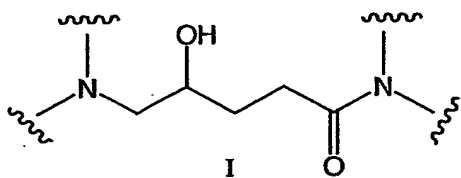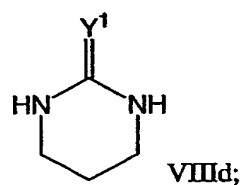
wherein Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached A_1 groups, and optionally substituted with one or more covalently attached A_2 groups;

A_1 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$, wherein W_3 is substituted with 1 to 3 A_3 groups;

A_2 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$;

A_3 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$;

X_2 and X_3 are independently a bond, $-O-$, $-N(R_2)-$, $-N(OR_2)-$, $-N(N(R_2)(R_2))-$, $-S-$, $-SO-$, or $-SO2-$;

each Y_1 is independently O, $N(R_2)$, $N(OR_2)$, or $N(N(R_2)(R_2))$, wherein each Y_1 is bound by two single bonds or one double bond;

R_1 is independently H or alkyl of 1 to 12 carbon atoms;

R_2 is independently H, R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, $-CN$, N_3, $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$, $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, $=O$, $=S$, $=N(R_1)$, $=N(R_{6b})$ or W_5;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups; or R_5 is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or

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alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-
containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_3 is W_4 or W_5;

W_4 is R_5, -C(Y_1)R_5, -C(Y_1)W_5, -SO$_2R_5$, or -SO$_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3
R_2 groups;

m1 is independently an integer from 0 to 12, wherein the sum of all m1's within each
individual claim of A_1, A_2 or A_3 is 12 or less;

m2 is independently an integer from 0 to 2; and

ᶴ indicates a site of covalent attachment of A_1 or A_2.

124.   The compound of claim 123 wherein:

A_1 is -(C(R_2)(R_2))$_{m1}$-W_3, wherein W_3 is substituted with 1 A_3 group;

A_2 is -(C(R_2)(R_2))$_{m1}$-W_3; and

A_3 is -(C(R_2)(R_2))$_{m1}$-P(Y_1)(Y_1R_{6a})(Y_1R_{6a}).

125.   The compound of claim 123 wherein W_3 is W_5, and W_5 is selected from:

-1694-
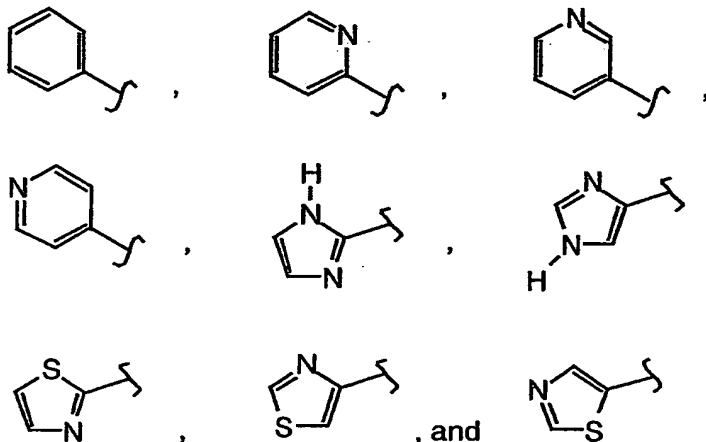
126.   The compound of claim 125 wherein W_5 is a pyridine heterocycle bonded to —$C(R_2)_2$— at the 2, 3, 4, 5 or 6 position.

5   127.   The compound of claim 125 wherein A_3 has a formula selected from:
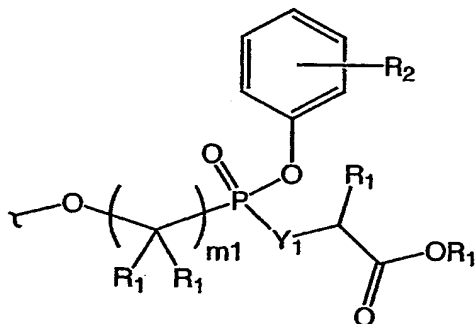
wherein m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R_2 groups.

10   128.   The compound of claim 125 wherein A_3 has a formula selected from:
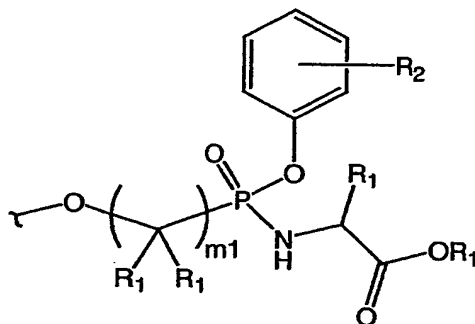
129.   The compound of claim 128 wherein A₃ has a formula selected from:
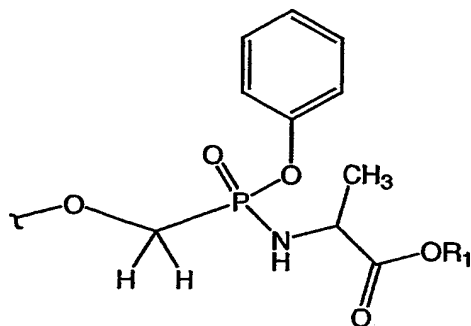
130.   A method of inhibiting the activity of HIV protease comprising the step of contacting a sample suspected of containing HIV with a composition of claim 1.

131.   The method of claim 130 wherein the HIV protease is *in vivo*.

132.   A method for the treatment or prevention of the symptoms or effects of HIV infection in an animal which comprises administering to said animal a formulation comprising a therapeutically effective amount of a compound according to claim 1.

133.   The method of claim 132 wherein the compound is formulated with a pharmaceutically acceptable carrier.

134.   The use of a compound of claim 1 to prepare a medicament for treatment of AIDS.

135.   The use of a compound of claim 3 to prepare a medicament for treatment of AIDS.

136.   The method of claim 133 wherein the formulation further comprises a second active ingredient selected from a nucleotide reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, an HIV protease inhibitor, and an HIV integrase inhibitor.

137. A process for preparing a compound of claim 1 wherein a compound comprising A^3 or a precursor to A^3 is reacted with an HIV protease inhibitor compound wherein the HIV protease inhibitor compound does not have a phosphonate group, whereby a compound of claim 1 is formed.

5

138. In an HIV protease inhibitor, the improvement comprising a substituent having a phosphonate or phosphonate prodrug.

139. The improved HIV protease inhibitor compound of claim 138 selected from:

10   a Saquinavir-like phosphonate protease inhibitor compound,

a Lopinavir-like phosphonate protease inhibitor compound,

a Ritonavir-like phosphonate protease inhibitor compound,

a Indinavir-like phosphonate protease inhibitor compound,

a Atazanavir-like phosphonate protease inhibitor compound,

15   a Nelfinavir-like phosphonate protease inhibitor compound,

a Tipranavir-like phosphonate protease inhibitor compound,

a Amprenavir-like phosphonate protease inhibitor compound,

a KNI-like phosphonate protease inhibitor compound, and

a Cyclic Carbonyl-like phosphonate protease inhibitor compound;

20   and pharmaceutically acceptable salts, hydrates, and formulations thereof.

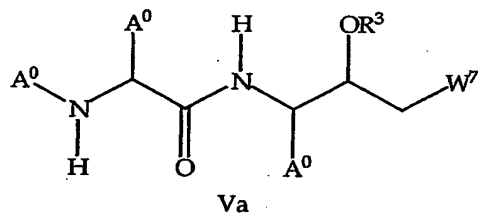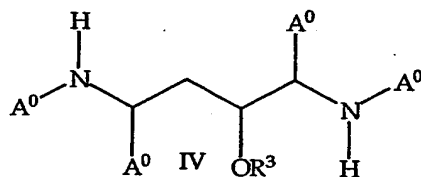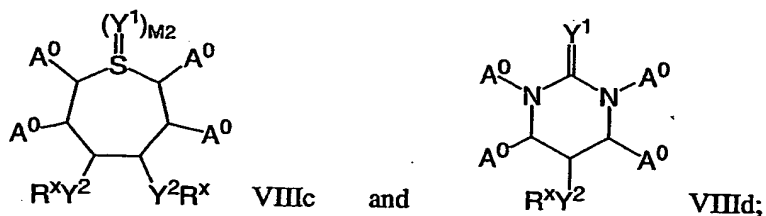140.   The improved HIV protease inhibitor compound of claim 138 of the Formulas:

Structure I

Structure II, X = C, SO

Structure III

Structure IV

Structure V

Structure VI

Structure Va

Structure VII

Structure VIIIa

Structure VIIIb

5

VIIIc   and   VIIId;

wherein:

A⁰ is A¹, A² or W³ with the proviso that the compound includes at least one A¹;

A¹ is:

A² is:

A³ is:

Y¹ is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

Y² is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)$_{M2}$-, or -S(O)$_{M2}$-S(O)$_{M2}$-;

R^x is independently H, R¹, W³, a protecting group, or the formula:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups, or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or -NO_2;

R^{3b} is Y^1;

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)$_2R^x$, -S(O)(OR^x), -S(O)$_2$(OR^x), -OC(Y^1)R^x, -OC(Y^1)OR^x, -OC(Y^1)(N(R^x)(R^x)), -SC(Y^1)R^x, -SC(Y^1)OR^x, -SC(Y^1)(N(R^x)(R^x)), -N(R^x)C(Y^1)R^x, -N(R^x)C(Y^1)OR^x, or -N(R^x)C(Y^1)(N(R^x)(R^x)) ;

R^{3d} is -C(Y^1)R^x, -C(Y^1)OR^x or -C(Y^1)(N(R^x)(R^x));

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, -C(Y^1)R^5, -C(Y^1)W^5, -SO_2R^5, or -SO_2W^5;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2 A^0 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

-1700-

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

141.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

5

, and
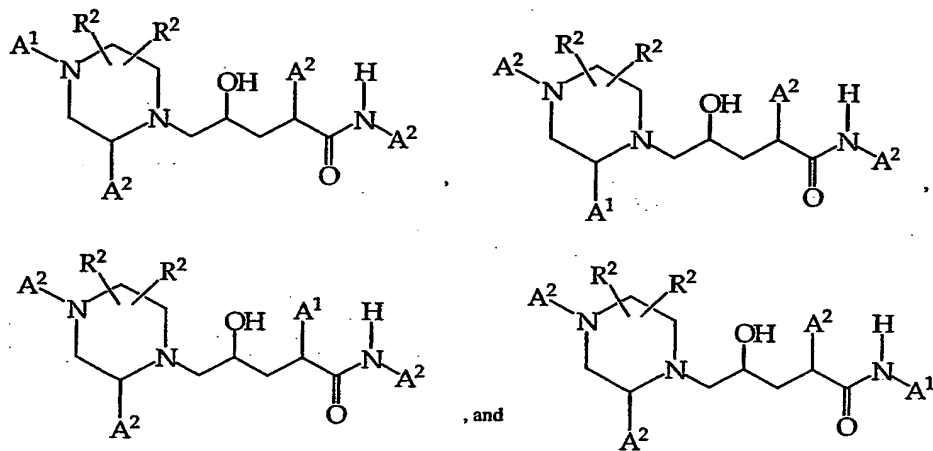
142.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:
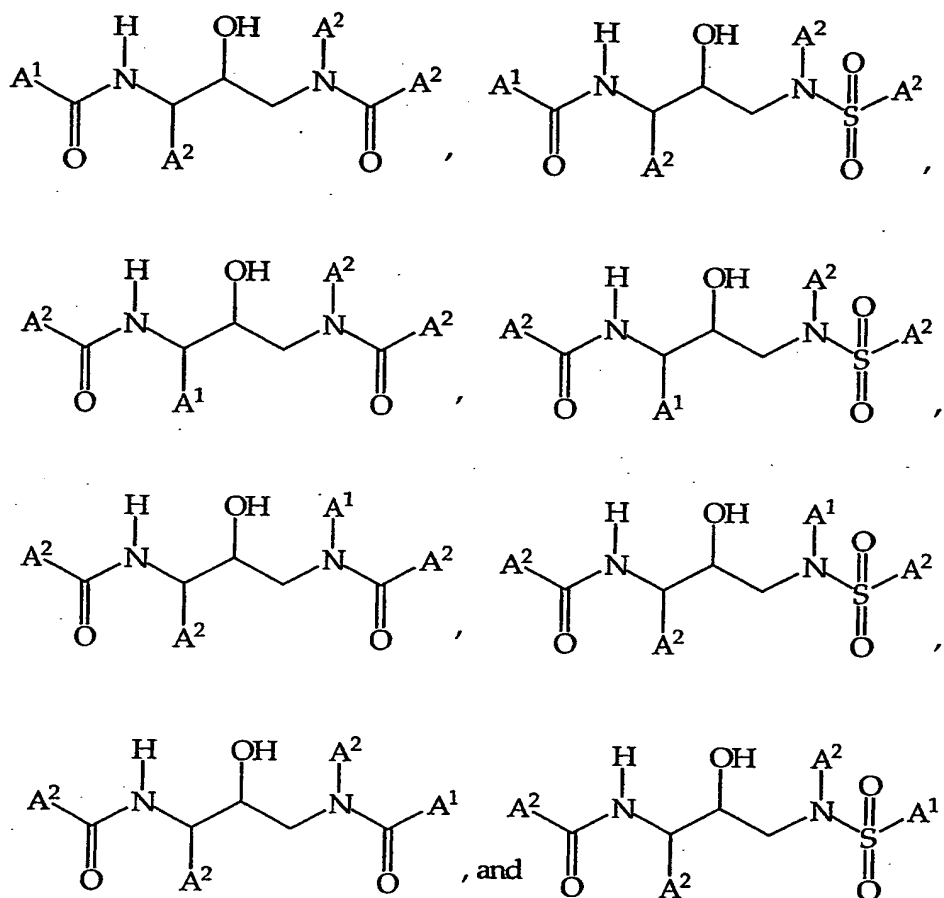
143.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

5
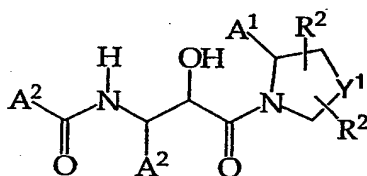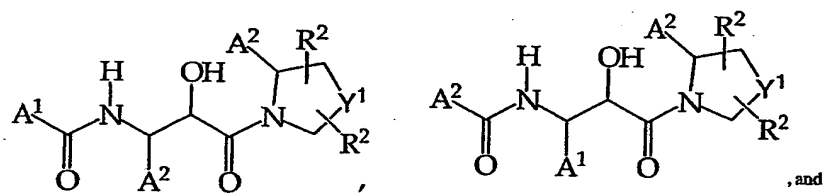
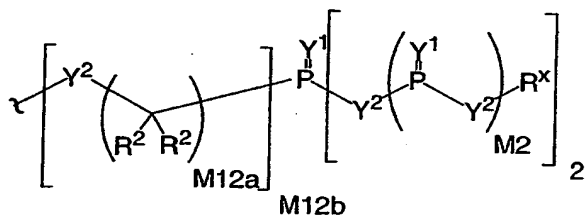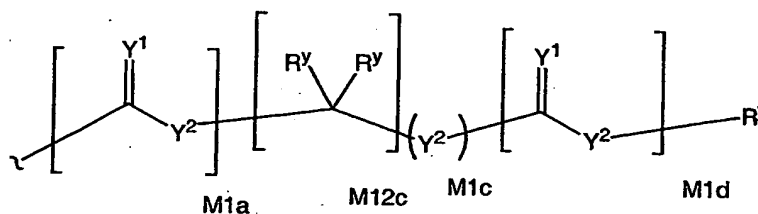144.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

and
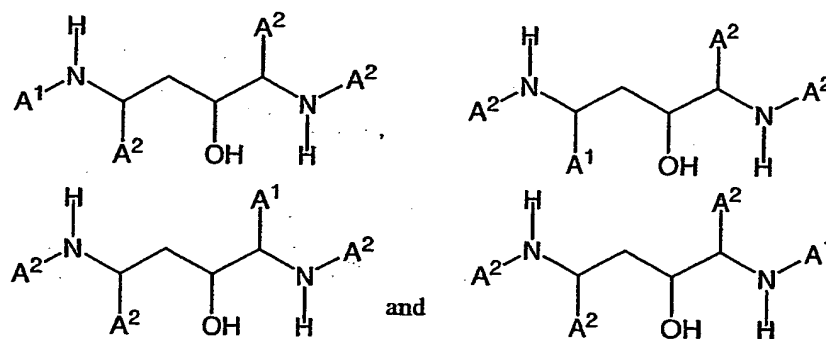
5   145.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:
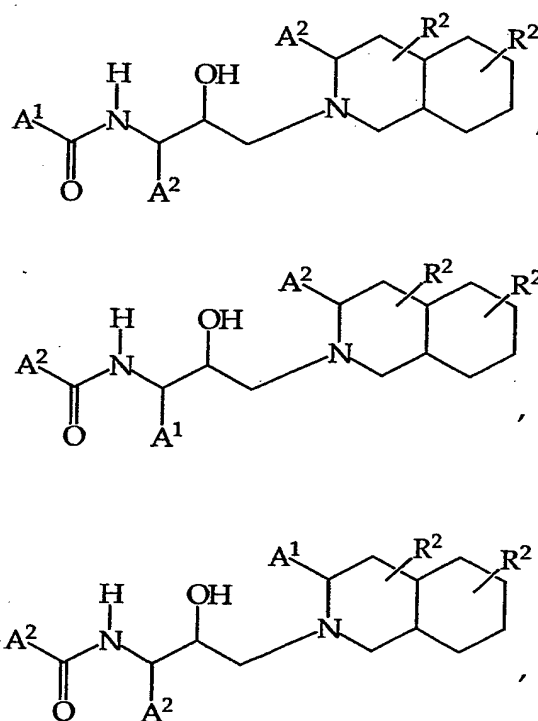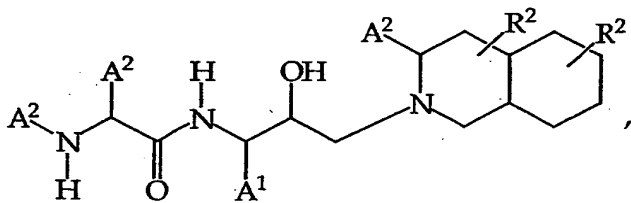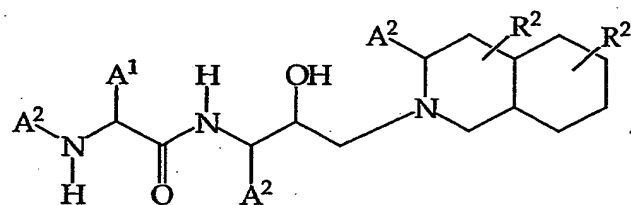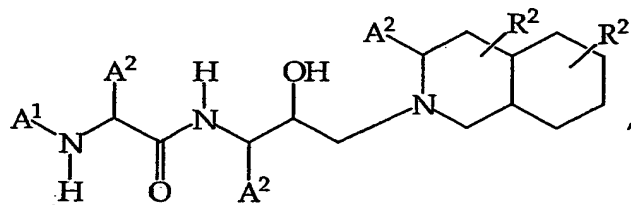
and
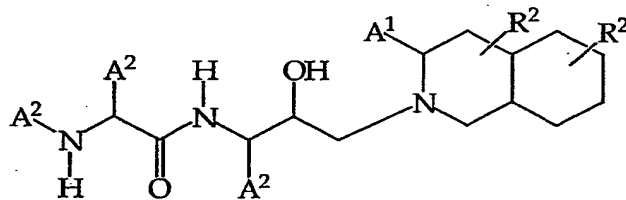
146.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:
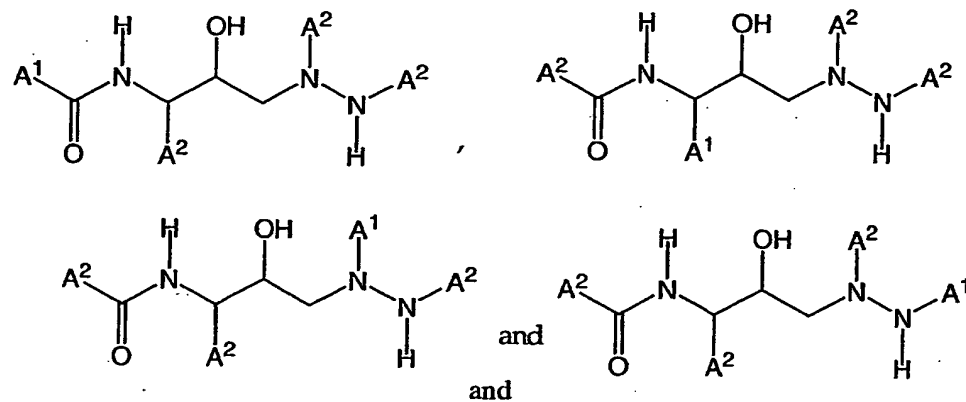
147.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

and
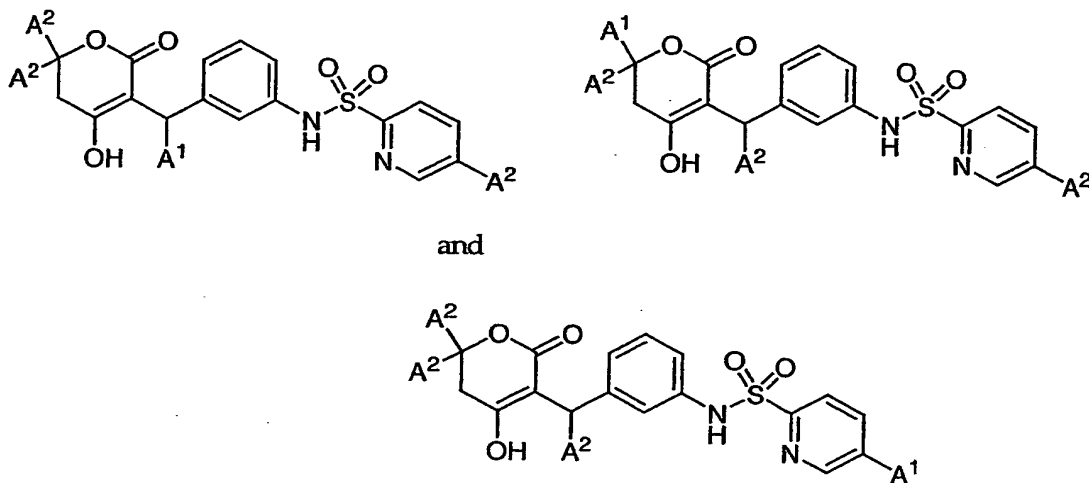
148.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

and
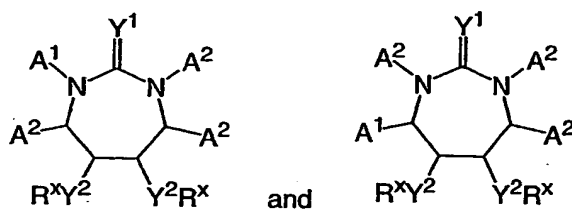
149.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

and

5
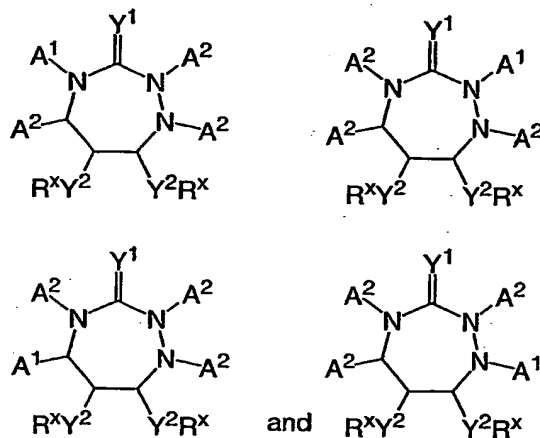
150.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

and
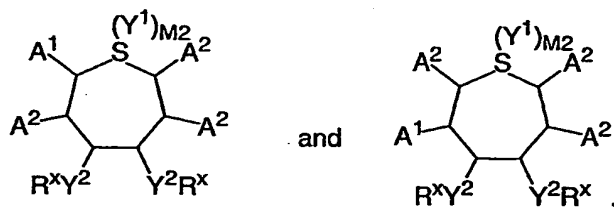
151.   The improved HIV protease inhibitor compound of claim 140 of the Formulas:

and
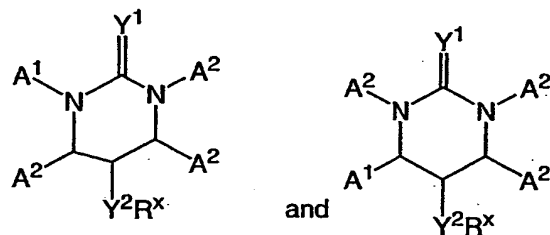
152.   In an HIV protease inhibitor not containing a phosphonate or phosphonate prodrug, the improvement comprising a substituent having a phosphonate or phosphonate prodrug.

5   153.   The improved HIV protease inhibitor compound of claim 152 selected from:
a Saquinavir-like phosphonate protease inhibitor compound,
a Lopinavir-like phosphonate protease inhibitor compound,
a Ritonavir-like phosphonate protease inhibitor compound,
a Indinavir-like phosphonate protease inhibitor compound,
10   a Atazanavir-like phosphonate protease inhibitor compound,
a Nelfinavir-like phosphonate protease inhibitor compound,
a Tipranavir-like phosphonate protease inhibitor compound,
a Amprenavir-like phosphonate protease inhibitor compound,
a KNI-like phosphonate protease inhibitor compound, and
15   a Cyclic Carbonyl-like phosphonate protease inhibitor compound;
and pharmaceutically acceptable salts, hydrates, and formulations thereof.

154. The improved HIV protease inhibitor compound of claim 152 of the Formulas:

I

II   X = C, SO

III

IV

V

VI

Va

VII

VIIIa


VIIIb

5

-1710-

VIIIc   and   VIIId;

wherein:

A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1;

A^1 is:

;

A^2 is:

;

A^3 is:

;

Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)$_{M2^-}$, or -S(O)$_{M2}$-S(O)$_{M2^-}$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:

M1a   M12c   M1c   M1d

;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with

5   0 to 3 R^3 groups, or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8

carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is

R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or -NO_2;

10   R^{3b} is Y^1;

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)$_2R^x$, -S(O)(OR^x), -S(O)$_2$(OR^x),

-OC(Y^1)R^x, -OC(Y^1)OR^x, -OC(Y^1)(N(R^x)(R^x)), -SC(Y^1)R^x, -SC(Y^1)OR^x,

-SC(Y^1)(N(R^x)(R^x)), -N(R^x)C(Y^1)R^x, -N(R^x)C(Y^1)OR^x, or -N(R^x)C(Y^1)(N(R^x)(R^x)) ;

R^{3d} is -C(Y^1)R^x, -C(Y^1)OR^x or -C(Y^1)(N(R^x)(R^x));

15   R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of

2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, -C(Y^1)R^5, -C(Y^1)W^5, -SO$_2R^5$, or -SO$_2W^5$;

20   W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3

R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and

independently substituted with 0, 1 or 2 A^0 groups;

25   M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

-1712-

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

155.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:

5
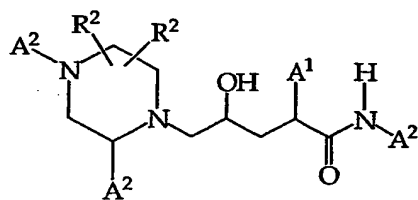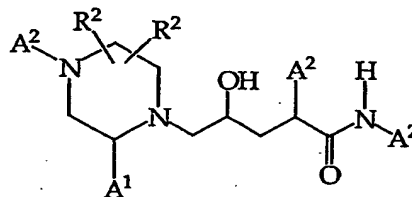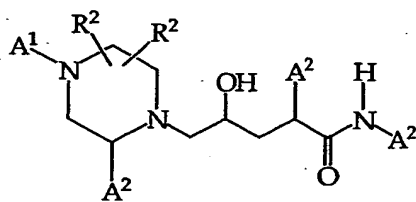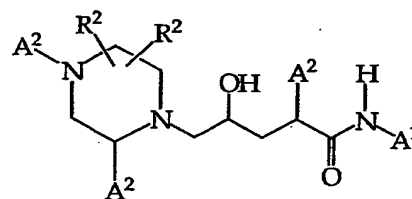
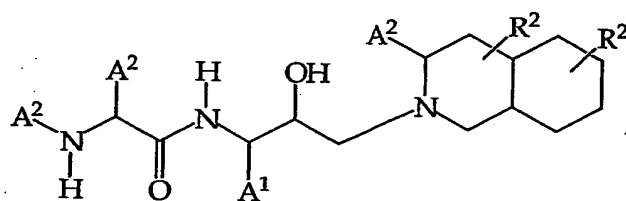156.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:
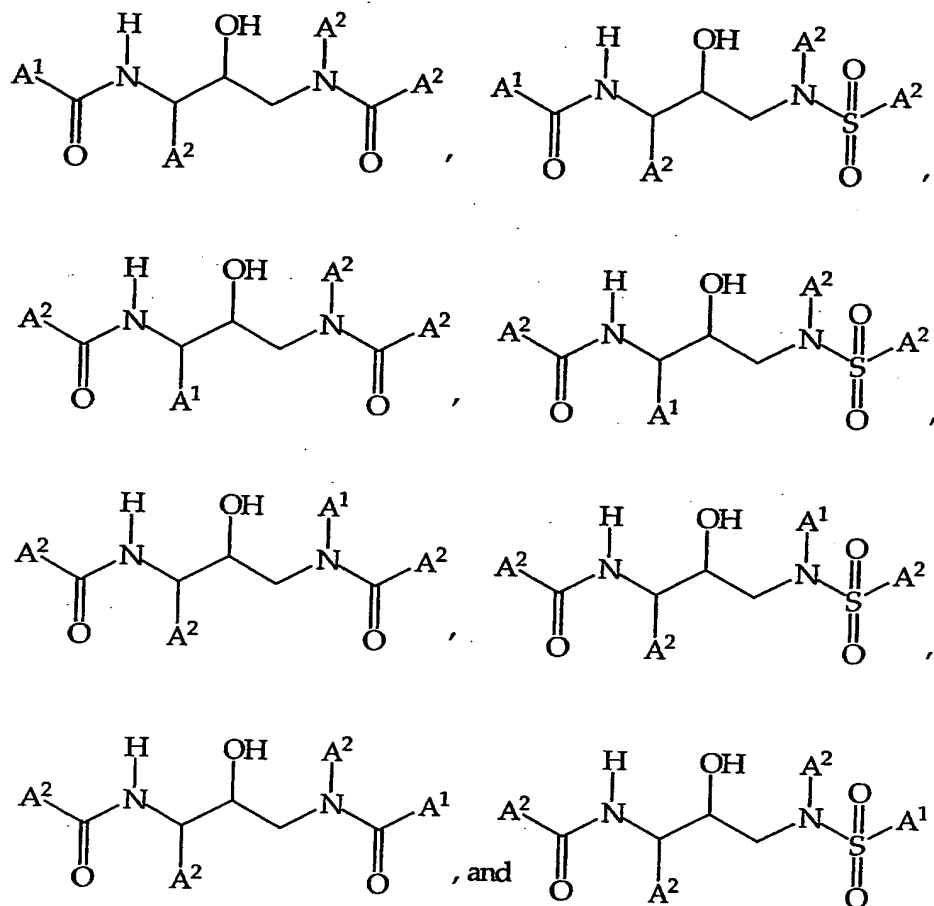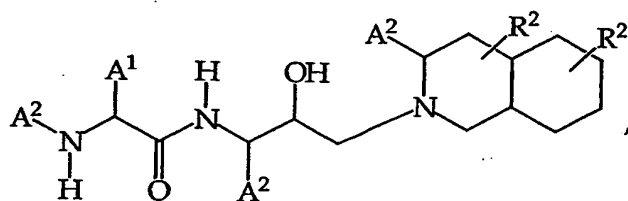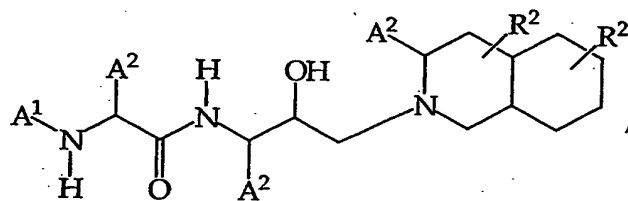

157.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:
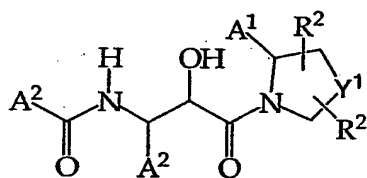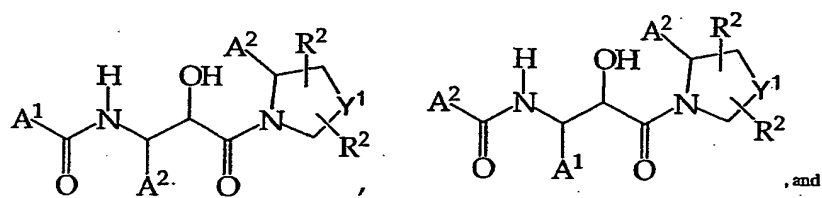
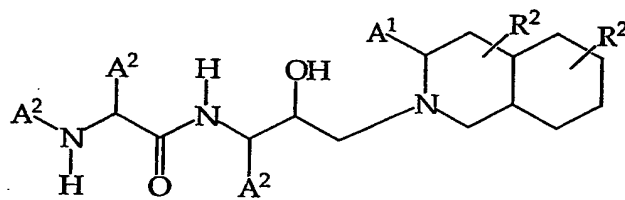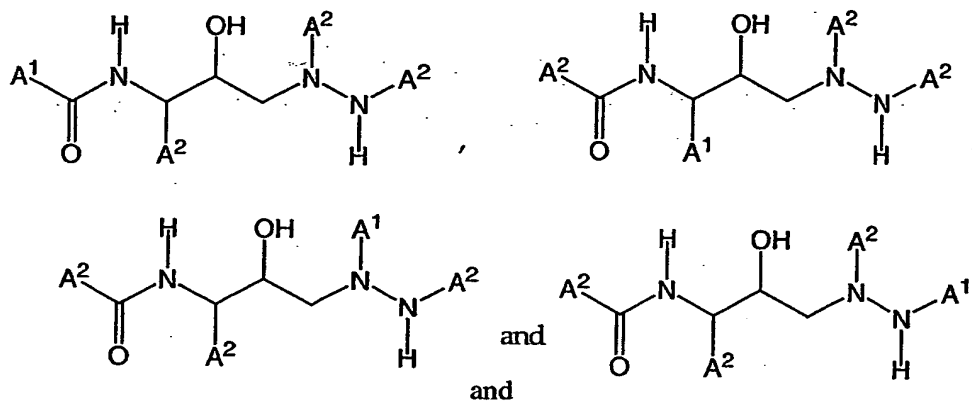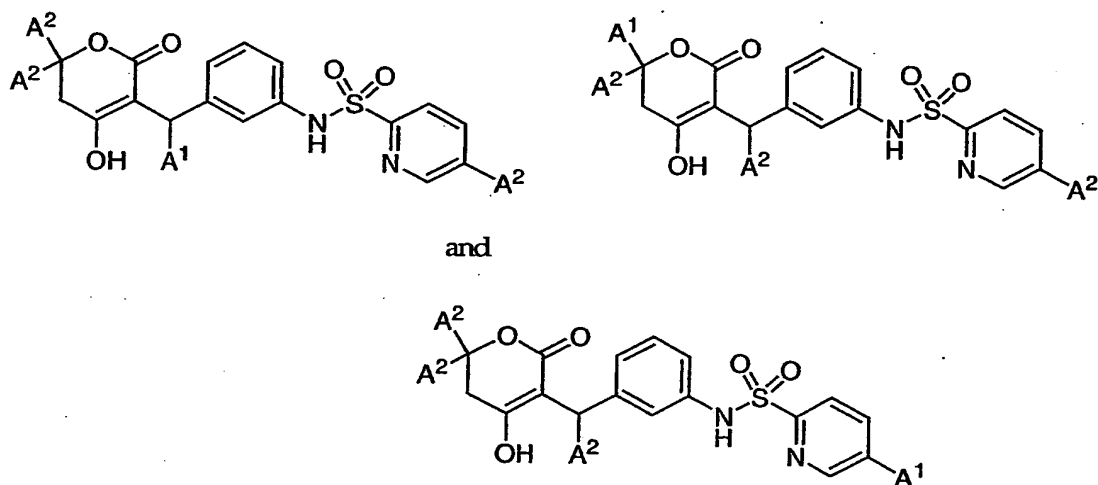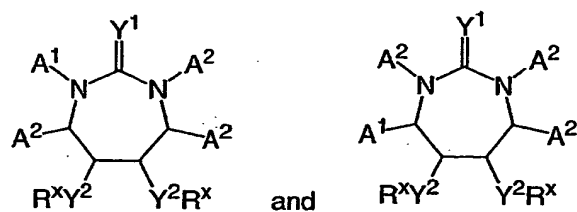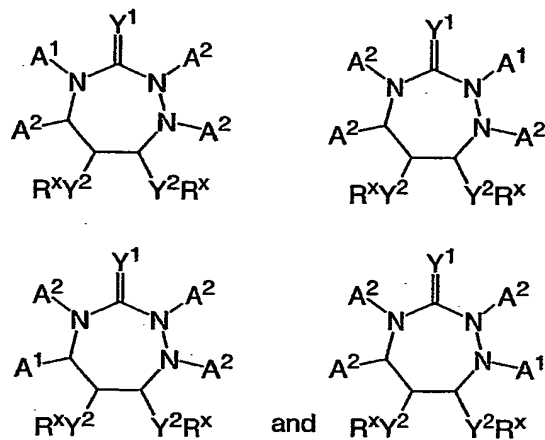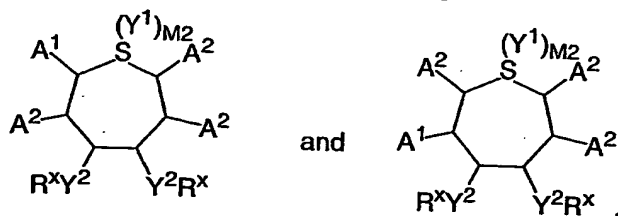158.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:

and
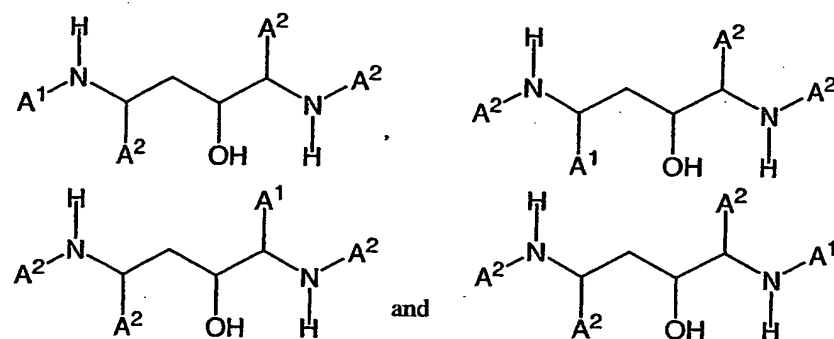
5   159.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:
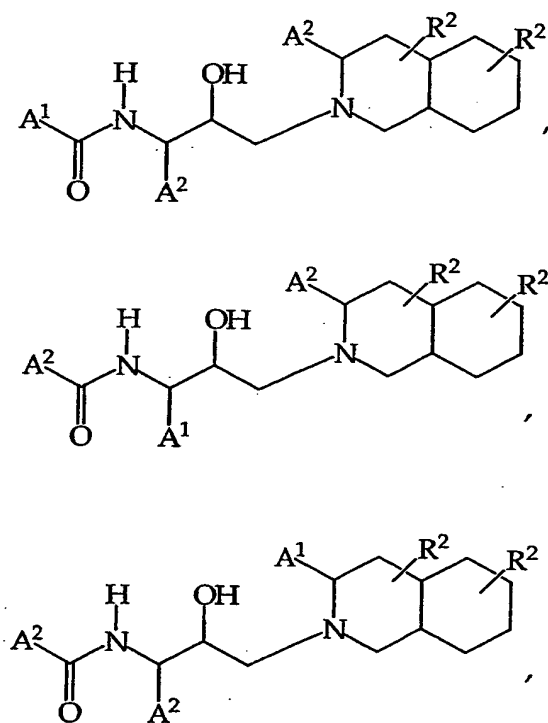
and

160.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:

,

,

and

and

161.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:

and

162.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:

and

163.   The improved HIV protease inhibitor compound of claim 154 of the Formulas:

and

164.　The improved HIV protease inhibitor compound of claim 154 of the Formulas:

and

5　　165.　The improved HIV protease inhibitor compound of claim 154 of the Formulas:

and
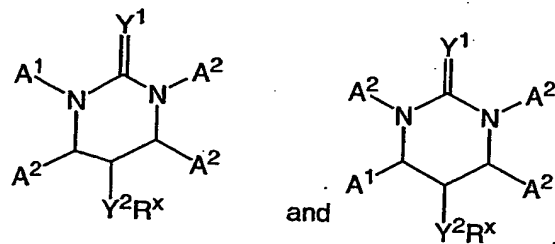
166. An MBF compound of Table 100.

167. A compound described herein.

5   168. A compound of Claim 167 described in the schemes or examples.

169. A method of making a compound described herein.

170. A method of Claim 169 described in the schemes or examples.

10

171. The use of a compound described here for treatment of HIV in humans.

172. The method of Claim 171 wherein the compound is described in the schemes or examples.

15

173 The use of a compound described here in the manufacture of a medicament.

174. The use of Claim 173 wherein the compound is described in the schemes or examples.

20

175. An HIV protease inhibitor compound capable of accumulating in human PBMCs.

176. The compound of Claim 175 further comprising a phosponate or phosphonate

25   prodrug.

177. The compound of Claim 176 wherein the phosphonate or phosphonate prodrug are of the formula A^3:

30   A^3 is:
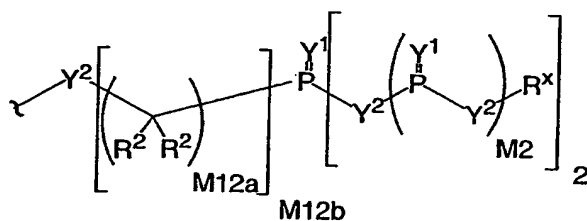
Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

5   R^x is independently H, R^1, W^3, a protecting group, or the formula:
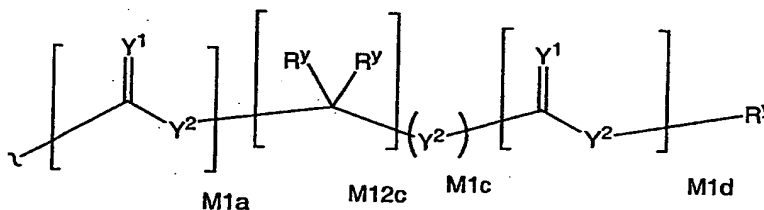
R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with

10   0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

15   R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of

20   2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

178.   The compound of Claim 177 wherein the intracellular half-life of the compound or an intracellular metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug.

179.   The compound of Claim 178 wherein the half-life is improved by at least about 50%.

180.   The compound of Claim 178 wherein the half-life is improved by at least about 100%.

181.   The compound of Claim 178 wherein the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug.

182.   The compound of Claim 181 wherein the half-life is improved by at least about 50%.

183.   The compound of Claim 181 wherein the half-life is improved by at least about 100%.

184.   The compound of Claim 181 wherein the half-life is improved by greater than 100%.

185. Use of a compound of the invention for the treatment of HIV infection.

186. Use of a compound of the invention in the manufacture of a medicament.

5   187. Use of a compound of the invention in the manufacture of a medicament for the treatment of disorders affecting white blood cells.

188. Method of treating a disorder affecting white blood cells, comprising:
administering a compound of the invention to a patient in need of white-blood-cell targeting.

10

189. Method of targeting a compound to white blood cells, comprising:
selecting a compound having a desired pharmaceutical activity and having a first structure;
modifying said first structure by replacing one or more atom of said first structure
15   with an organic substituent comprising a phosphonate group or incipient phosphonate group to provide a compound having a second structure.

190. A method of manufacturing a non-nucleoside compound having both selectivity for white blood cells and a desired pharmaceutical activity, comprising:
20   chemically synthesizing a first molecule having a first structure containing a phosphonate or incipient phosphonate group, wherein said first structure differs from a second structure of a compound known to have said desired pharmaceutical activity by having at least one hydrogen atom of said second structure replaced by an organic substituent comprising a phosphonate group or incipient phosphonate
25   group.

191. The method of claim 190, wherein said first molecule is synthesized by a series of chemical reactions in which a hydrogen of said second structure is replaced by said organic substituent.

30

192. The method of claim 190, wherein said first molecule is synthesized by a series of chemical reactions that never includes a molecule of said second structure.

193. Method of accumulating an HIV protease inhibitor inside a white blood
35   cell, comprising:
administering to a sample a composition comprising a compound of the invention.

194.   The method of Claim 193 wherein said sample is a patient.

40

195. The method of claim 193, wherein said compound of the invention has a chemical structure A-B, wherein (a) a compound having structure A-H has HIV protease inhibitor activity and (b) substructure B comprises a phosphonate group or incipient phosphonate group.

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196. Method of increasing half-life of a non-nucleoside compound having anti-retroviral activity, comprising:

replacing at least one hydrogen atom or organic radical of said compound by an organic substituent comprising a phosphonate group or incipient phosphonate.

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197. Method of designing a drug having specificity for white blood cells for synthesis, comprising:

obtaining a first list of first compounds having a desired activity;

creating a second list of second compounds, each of said second compounds having a structure in which at least one hydrogen atom or organic radical of a compound of said first list has been replaced by an organic substituent comprising a phosphonate group or incipient phosphonate group; and

selecting a synthetic pathway capable of producing some or all of said second compounds from available starting materials, thereby providing a third list of compounds and associated synthetic techniques.

198. Method of manufacturing a pharmaceutical composition having said specificity of claim 197, comprising:

synthesizing a compound selected from said third list using said associated synthetic technique; and

admixing said synthesized compound with a pharmaceutically acceptable carrier.

199. A composition produced by the method of claim 198.

200. Method for producing a pharmaceutical composition having specificity for white blood cells, comprising:

admixing a therapeutically effective amount of a compound of the invention with a pharmaceutically acceptable carrier.